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PUBLIC HEALTH SERVICE
THOMAS PARRAN, *Surgeon General*

A BRIEF HISTORY
OF BACTERIOLOGICAL INVESTIGATIONS
OF THE
UNITED STATES PUBLIC HEALTH SERVICE

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It contains (1) current information regarding the prevalence and geographic distribution of communicable diseases in the United States insofar as data are obtainable, and of cholera, plague, smallpox, typhus fever, yellow fever, and other important communicable diseases throughout the world; (2) articles relating to the cause, prevention, and control of disease; (3) other pertinent information regarding sanitation and the conservation of the public health.

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A BRIEF HISTORY OF BACTERIOLOGICAL INVESTIGATIONS OF THE UNITED STATES PUBLIC HEALTH SERVICE

By A. M. Stimson, *Medical Director, United States Public Health Service*

INTRODUCTION[1]

The Public Health Service of the United States is one of the oldest of our Government organizations, dating from 1798. Originally established to give medical relief to seamen of the merchant marine, and consisting of a few hospitals administered from a central office in the Treasury Department, it has experienced a gradual transition into an agency whose paramount duty is the protection and advancement of the health of the citizenry of the country, insofar as this is possible under our system of government. This transition is reflected in the successive names which the Service has borne: First, the "Marine Hospital Service," then, from 1902 to 1912, the "Public Health and Marine Hospital Service," and, since the latter date, the "Public Health Service." It must not be thought that the changes of function have coincided with those in the name of the Service—in fact the former always antedated the latter; nor is it true that the original purpose has been abandoned. On the contrary, the relief element has steadily broadened and improved until, at the present time, the splendidly housed and equipped and efficiently managed marine hospitals should be a source of pride for the Nation.

Among the added functions legally assigned to the Public Health Service which have affected the nature and direction of its bacteriological studies, the following are enumerated: The Federal quarantine service, which has demanded first-hand information leading to the detection of the quarantinable diseases and to the prevention of their dissemination; the medical inspection of alien immigrants, which has made similar demands concerning a greater range of disorders; the Federal control of biologic products, which has required much original research; the extension of aid to State health agencies,

[1] Editorial Note: In 1936, the Committee on Archives of the Society of American Bacteriologists undertook the compilation of material for a history of the development of bacteriology in America. Dr. Barnett Cohen, Archivist of the Society, requested the Surgeon General to have prepared, as one chapter in the compilation, a brief history of the bacteriological work of the Public Health Service and Medical Director A. M. Stimson was assigned to the task. After the manuscript had been completed, it was found that publication would be delayed, and permission was secured from Dr. Cohen for the publication of this material by the Public Health Service.

calling for much epidemiological, and consequently bacteriological, work; the prevention of the interstate spread of disease; and the study of stream pollution and purification, which is mainly an interstate and, hence, a Federal problem.

These and other functions have largely determined the direction of the research work of the Public Health Service. In compiling the following notes on the history of bacteriology in the Service, some difficulty has been experienced in deciding just what to include and what to omit. Although text books on bacteriology commonly contain some notes on the protozoa, these organisms are not in any sense bacteria, and consequently the very extensive work of the Service on malaria, and the recent and very interesting work on amebiasis, have been omitted. Certain outstanding epidemiological studies, such, for example, as that of tetraethyl lead poisoning, radium poisoning, and the dust studies in industrial hygiene, have involved little if any bacteriology, and are obviously not germane to the subject; while, on the other hand, pellagra, now recognized as a nutritional disease, required much negative bacteriological work for its elucidation, and has been included.

The plan in assembling these notes has been, first, to give some attention to the places in which the work has been done and the publication in which it has been reported, and then to present a discussion by topics alphabetically arranged and each considered more or less chronologically.

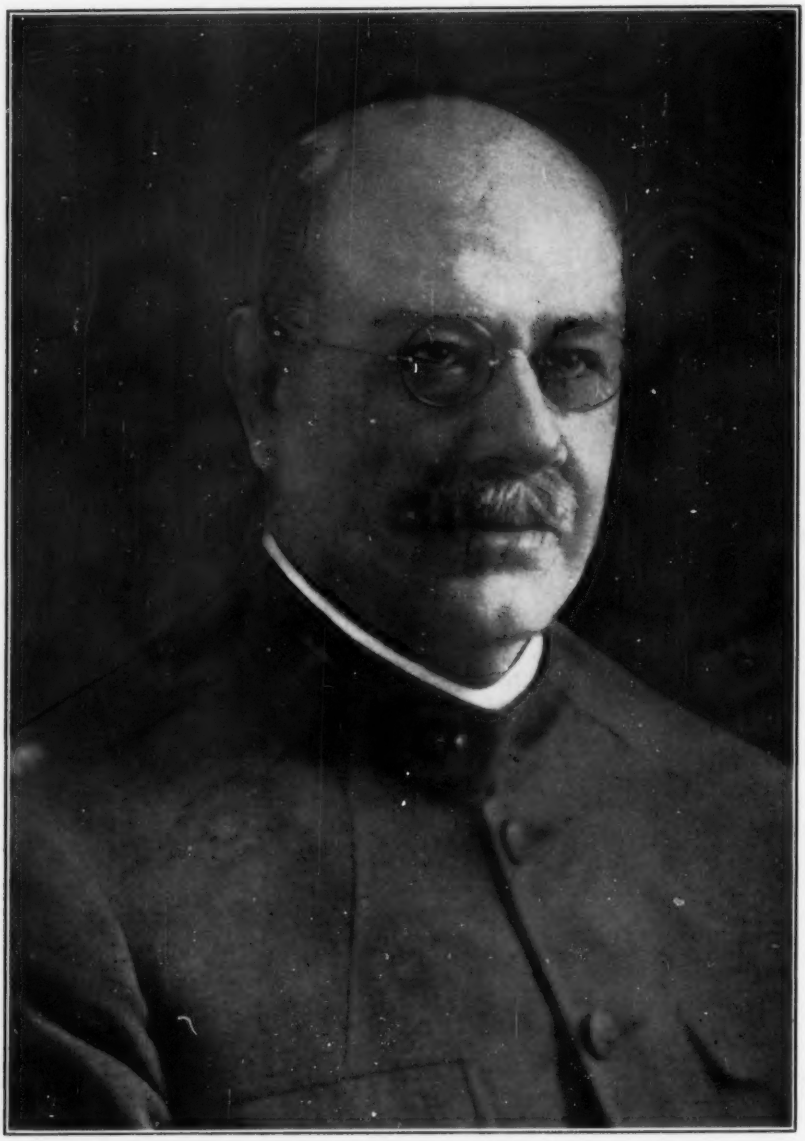
THE HYGIENIC LABORATORY

"Great oaks from little acorns grow." The acorn in this case was a single large room situated on the ground floor of the marine hospital building at Stapleton, Staten Island, N. Y. In August 1887 a "laboratory of hygiene" was established there and Dr. Joseph J. Kinyoun was placed in charge, thus becoming the first director. It was reported with considerable pride that the apparatus was modeled after that used by Dr. Koch and included the latest Zeiss lenses. It was here that the Public Health Service first made its official acquaintance with bacteria. During the first year the cholera organism was demonstrated among passengers on two steamships arriving at that port. It will be recalled that at that time very little bacteriological work was being done in the United States. In England the first laboratory and teaching course for bacteriology was set up at King's College about this time. Germany and France were being invaded by large numbers of young foreign doctors, including some Americans, who came to learn about the new and somewhat mystical science.

The laboratory remained at Stapleton only about 4 years. In June 1891 it was removed to the top floor of the Butler Building on Capitol Hill in Washington, which had just become the headquarters of the

The old Marine Hospital at Stapleton, N. Y., in one room of which the Hygienic Laboratory had its beginnings in 1887

The Butler Building, Washington, D. C., on the top floor of which the Hygienic Laboratory was housed when it was first moved to that city.



Dr. Joseph J. Kinyoun, who as a young officer of the Marine Hospital Service initiated the labora.ory work which led to the establishment of the Hygienic Laboratory, now the National Institute of Health. Doctor Kinyoun, the first director, was in charge of the Hygienic Laboratory from August 1887 to April 30, 1899.

Marine Hospital Service. During these few years, as has generally been the case since, the bulk of the work dealt with problems encountered by the Service, of which the laboratory was a part. Experiments on disinfectants to be used in quarantine work early demonstrated the advantage of sulphur dioxide over other gases. Familiarity was acquired with the known organisms of cholera, tuberculosis, typhoid fever, pneumonia, anthrax, malaria, and suppuration.

In 1891 Dr. Kinyoun was sent to Europe and took courses under Koch, whose tuberculin, still of unrevealed composition, was being tried out rather indiscriminately on the crowds of consumptives who had flocked to Berlin on the circulation of a rumor that a "cure" had been devised. Kinyoun commented that it was evident from the first that the agent was capable of doing great harm as well as good. He saw much of the bacteriological work being conducted at that time in Berlin. Then he studied rabies at the Pasteur Institute in Paris, and heard Metchnikoff on phagocytosis. He returned full of ideas which became reflected later in his initiation of and recommendations regarding laboratory and public health activities of the Service, many of which were successfully carried out by his successors. In bacteriology he appears to have been solid, dependable, and industrious. These qualities were more needed at that time in the history of the organization than great brilliance or originality. As regards vision in public health matters, we believe that Dr. Kinyoun deserves a still higher place. For example, such measures as the Government standardization and control of the manufacture and sale of biological preparations used in medicine, the maintenance of a graduate school in public health laboratory methods, the examination and purification of public water supplies, the sanitation of common carriers, the establishment of separate divisions in the Hygienic Laboratory, the modernization of quarantine equipment, the defense of animal experimentation, the determination of the usefulness of disinfectants, and other farsighted and useful activities appear, from the record, to have been initiated by him. In 1894 he studied diphtheria antitoxin in Berlin and Paris, and on his return became one of the pioneers in the production and introduction of that substance in America. He was relieved from duty as director in 1899, being succeeded by Dr. M. J. Rosenau. He will be mentioned later in connection with the first plague outbreak in San Francisco. It was he, by the way, who had opposed the acceptance of Sanarelli's *B. icteroides* as the cause of yellow fever, until the following objections should be explained away: the close resemblance to other intestinal organisms, the seasonal prevalence of yellow fever, the fact that the lesions produced in lower animals differed from those of human yellow fever, the fact that, although the bacillus was pathogenic to animals by laboratory inoculation, such animals were not susceptible

to yellow fever during epidemics, and that, since *B. icteroides* was viable in water, there should be water-borne epidemics of yellow fever. These criticisms have remained unanswerable, and should apparently have had more weight with the advocates of Sanarelli's organism.

The quarters at the Butler Building were recognized even at the beginning as being too small, cramped, and generally unsuitable for laboratory purposes and steps were taken to secure appropriations for a separate building. In 1903 such a building was provided on a site of 5 acres near the western end of E Street NW., transferred from the Navy Department. Additions have been made to the plant from time to time until now it consists of four buildings totalling some 10 times the cubic space of the original building on this site. Plans are under way for the removal of the entire institution to Bethesda, Md., several miles outside the city, and some of the new buildings were occupied during the latter part of 1938. The name of the institution was changed by an act of Congress (May 26, 1930) to the National Institute of Health.

OTHER RESEARCH INSTITUTIONS

It must be realized that the National Institute of Health (Hygienic Laboratory), while it is the most important research laboratory of the Public Health Service with reference to size and number of employees, is not the only such laboratory for research (including bacteriological studies) conducted by the Service. A number of temporary laboratories have been set up in the field for various investigations, and the marine hospitals are all provided with clinical laboratories, in some of which research has been conducted. In addition, a plague laboratory has been maintained almost continuously in San Francisco since the first outbreak of plague there; a laboratory for the study of spotted fever and other diseases at Hamilton, Mont., has been in almost continuous operation since the Service became interested in spotted fever in that State, and a laboratory for the exclusive investigation of stream pollution and sewage disposal has been in operation at Cincinnati for many years. Research work on leprosy has been conducted at Honolulu, the island of Molokai, and the leprosarium at Carville, La. Work performed in these various laboratories will be mentioned later.

DIVISION OF SCIENTIFIC RESEARCH

As the research work of the Public Health Service grew, with the imposition of new duties and the granting of new authorities, it became necessary to send out working parties on various research problems, many of which were not under the administrative control

of the Hygienic Laboratory. To coordinate these and act as a central agency for research work within the Service, a Division of Scientific Research was created in 1901, with Asst. Surg. Gen. H. D. Geddings

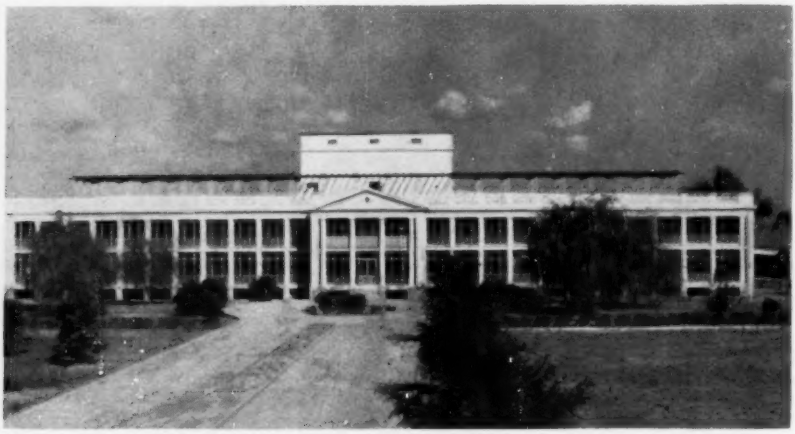
Old South Building of the present National Institute of Health.

as its first chief. He was a man of wide cultural and scientific interests, having had European training in laboratory methods, and being identified with much of the early work of the Hygienic Laboratory.

New laboratory of the present National Institute of Health.

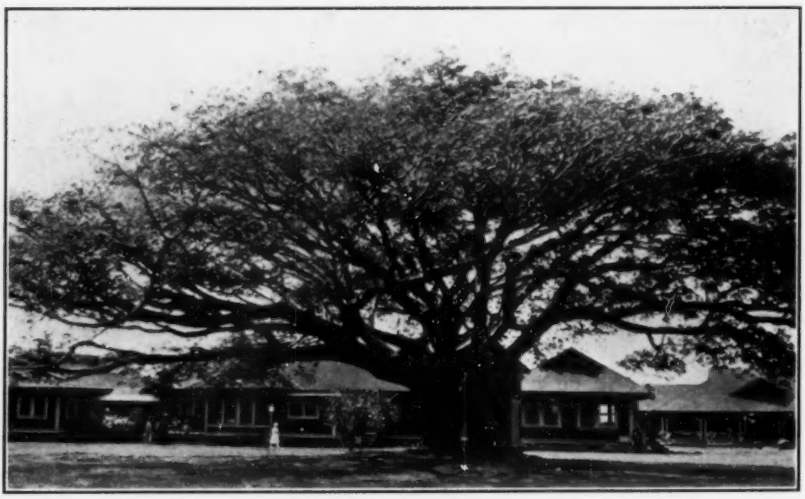
His lapse in connection with the etiology of yellow fever, elsewhere referred to, should not be permitted to overshadow his very considerable services to science, nor the prestige which his dignified and able presentations at scientific meetings here and abroad undoubtedly brought to the Public Health Service.

All of the successors to the positions of Director of the Hygienic Laboratory and of Chief of the Division of Scientific Research are living at the present time; and while, in compliance with usual cus-



Infirmary at the National Leprosarium, Carville, La.

tom, biographical allusions will be omitted, their more notable contributions at least will be referred to. They were, for the Hygienic Laboratory, M. J. Rosenau, John F. Anderson, George W. McCoy, and L. R. Thompson, and for the Division of Scientific Research,



Compound at Kalihi Hospital, Honolulu. Spreading monkey-pod tree, with telephone booth underneath.

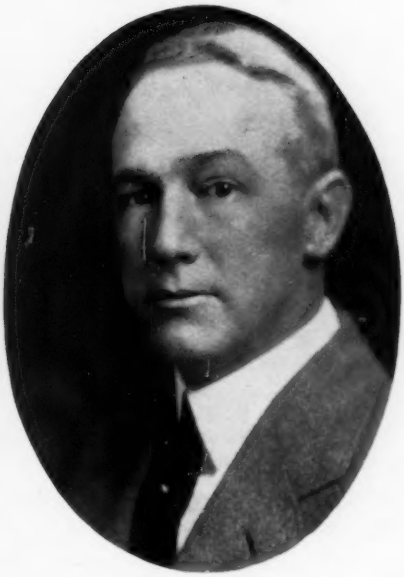
John M. Kerr, Joseph W. Schereschewsky, A. M. Stimson, and L. R. Thompson.

The fact has been alluded to, but will bear reiteration, that the research work of the Public Health Service is best understood when

Dr. M. J. Rosenau

Dr. John F. Anderson

Dr. Geo. W. McCoy



Dr. L. R. Thompson

Other directors of the National Institute of Health (and Hygienic Laboratory) and terms of office.

Doctor Rosenau, May 1, 1899–September 30, 1909. Now professor of preventive medicine, University of North Carolina, Chapel Hill, N. C.

Doctor Anderson, October 1, 1909–November 19, 1915. Now vice president of E. R. Squibb & Sons, New York, N. Y.

Doctor McCoy, November 20, 1915–January 31, 1937.

Doctor Thompson, February 1, 1937–

seen against the background of the legally imposed and imperative duties of the Service. These deal with a multiplicity of activities, all of which affect in some way the health of the people, but many of which have only remote or casual relation to bacteriology. The sciences of chemistry, pharmacology, animal parasitology, epidemiology and vital statistics, and genetics and sociology may, in many cases, be more intimately bound up with these activities. Again, while there are no set limitations, legal or otherwise, against the prosecu-

Placing the cornerstone of the new National Institute of Health Administration Building at Bethesda, Md., June 30, 1938. Left to right—Secretary of the Treasury Henry Morgenthau, Jr., Mrs. Luke Wilson, whose husband donated the site, and Surgeon General Thomas Parran.

tion of pure research in subjects dealing with medicine and public health, it is natural that with so many and such pressing practical problems confronting it, the Service should turn to its laboratory first of all for their solution. Often, however, these practical studies have opened up large fields of general theory whose further exploration in the interest of medicine seemed imperative. As an example may be cited the case of anaphylaxis. This was of interest when first observed chiefly in connection with the administration of serums, with the control of which the Service was legally identified, but the

phenomenon brought to light largely by the work of Service investigators has assumed a prominent place in the theory of pathology.

Many of the early contributions of the Hygienic Laboratory were published in the annual reports of the Public Health Service, but, beginning with 1900, they appeared officially in the bulletins of the Hygienic Laboratory. Officers have been permitted also to publish their reports in various professional and scientific periodicals. Short, timely articles have frequently been published in the weekly Public Health Reports and issued as separates, and an occasional contribution to bacteriology has been printed as a Public Health Bulletin. The supplements to the Public Health Reports also contain some articles of bacteriologic interest. The publication known as Venereal Disease Information, while most valuable to all workers in this specialty, is more of the nature of a "Zentralblatt," and original articles, at least of a bacteriological nature, appearing therein are relatively few.

The following simple method of referring to Public Health Service publications in this monograph is believed to be adequate for identification: Dates are italicized; publication numbers are printed in roman type.

AR=Annual reports of the Public Health Service.
HLB=Hygienic Laboratory bulletins.
NIHB=National Institute of Health bulletins (continuation of the Hygienic Laboratory bulletins).
PHB=Public Health bulletins.
PHR=Public Health Reports (published weekly).
RPHR=Reprints from the Public Health Reports.
SPHR=Supplements to the Public Health Reports.
VDI=Venereal Disease Information.
RVDI=Reprints from Venereal Disease Information.

A. M. S.

ANAPHYLAXIS

Workers at the Hygienic Laboratory were pioneers in the American development of anaphylaxis. Their interest in the problem was twofold: First, no doubt, it was stimulated by responsibility to protect the public as much as possible from any deleterious effects of administering biological products; second, it was a new and highly interesting phenomenon of general pathology. While the modern applications to the theory and practice of medicine could not possibly have been foreseen, a working basis for their interpretation was laid down. The nature of these studies is indicated by the titles of published articles: "A study of the cause of sudden death following the injection of horse serum," by Rosenau and Anderson (HLB 29, *1906*); "(1) Maternal transmission of immunity to diphtheria toxine; (2) Maternal transmission of immunity to diphtheria toxine and hypersusceptibility to horse serum in the same animal," by Anderson (HLB 30, *1906*); "Studies upon hypersusceptibility and immunity," by Rosenau and Anderson (HLB 36, *1907*); "Further studies upon anaphylaxis," by Rosenau and Anderson (HLB 45, *1908*); the same title and authors (HLB 50, *1909*); "Studies upon anaphylaxis with special reference to the antibodies concerned," by Anderson and Frost (HLB 64 *1910*); and "Physiological studies in anaphylaxis," by W. H. Schultz (HLB 80, *1912*).

Following this series of studies the subject of anaphylaxis and hypersusceptibility in general became common property of workers at the Hygienic Laboratory in many different research connections, and we may have occasion to refer to some applications in the discussion of other topics.

ANTHRAX

Anthrax is a disease of relatively little public health importance in the United States, since only 100 to 200 cases occur annually; but such obvious precautions as can be taken without disproportionate expense to avoid the infection are legally observed by both the Department of Agriculture and the Public Health Service. The latter has been importuned at times to establish and maintain costly mechanisms for the disinfection of all suspected materials on entry into the country; but, on considering the fact that money expended in this way to avoid an occasional infection could be spent much more advantageously in combating some major health menace, and the further fact that there are many anthrax spores already indigenous to the country, it has adopted other means of control. These place upon

importers and interstate shippers the burden of compliance with certain regulations calculated to limit the spread of infectious materials.

In 1914 the question of whether or not anthrax could be transmitted by the bites of flies was still unsettled; and Mitzmain performed some animal experiments which demonstrated that both the stable fly *Stomoxys calcitrans* and the gadfly *Tabanus striatus* could transmit the infection if allowed to bite animals during the period of bacteriemia. He also demonstrated the persistence of the organism in the feces of the flies (HLB 94, *1914*).

During the World War a number of anthrax infections of the facial skin were observed among American troops and civilians. The absurd cry was raised in some quarters that it was another attempt on the part of the enemy to disable American soldiers by introducing infected shaving brushes. The source of the infection, was, indeed, traced at the Hygienic Laboratory to brushes containing the spores of anthrax, but the reason for their unusual prevalence appears to have been merely the disturbance in trade channels which had permitted the use of infected crude materials without the disinfection previously practiced. The infected brushes were chiefly cheap articles made of horsehair (RPHR 523, *1919*), (AR *1918*, p. 60). Under suitable regulations issued at this time the menace shortly subsided.

BIOLOGICS CONTROL

Under this title will be considered the bacteriological activities incidental to the legal control of the manufacture and sale of products used in the prevention and treatment of human diseases, such as serums, vaccines, viruses, and the like. This control is vested by law in the Treasury Department, and the work of inspection, testing, and incidental research is performed by the Public Health Service. It applies to interstate and international transactions; but since there are few manufacturers desiring to engage only in intrastate business, it covers practically the whole field. Under the act of Congress passed in 1902 (U. S. Code, title 32, sec. 141), regulations were promulgated February 21, 1903, which became effective 6 months later. In brief, the law provides that all manufacturers desiring to engage in interstate or international traffic in products of this nature must hold a valid Treasury Department license. Such licenses are issued only after approval, by the Public Health Service, of the equipment, scientific competency of the personnel, and methods employed, and after searching tests of the products. The license does not, however, pretend to guarantee the effectiveness of all prod-

ucts. In many cases it would require superhuman wisdom to be able to state whether a given product is really an effectual preventive or cure for the disease for which it is intended. Bacteriologists are familiar with the extreme difficulty which attends the determination with scientific precision of the effectiveness of preparations of this class when applied to human beings. The effects on animals under experimental conditions cannot always be applied without question to human beings under natural conditions. Moreover, in many instances even the evidence of animal experimentation is lacking or imperfect, although the experience of physicians may be favorable, and they may desire to have such products available to them in their practice.

Wherever it has been possible to establish standards of potency, as in the case of the antitoxic sera, such standards have been promulgated, and rigid adherence to them has been insisted upon. In many cases, however, no such standards are possible, and the licenses indicate merely that the preparations have been prepared by sufficiently trained personnel in proper surroundings, by approved methods, and that the products themselves have proved upon testing to be what they are claimed to be, and to be free from dangerous impurities or contamination.

On the other hand, when licenses for new preparations are applied for, an earnest attempt is made to determine whether or not the claims for effectiveness are based upon scientific evidence. In many instances the claims have been found insufficiently grounded, and in a few apparently fraudulent, and licenses have been refused. Again, when batches of preparations have been found on testing to be below standard or contaminated or otherwise in conflict with regulations, the issue has been forbidden or the product withdrawn from the market. In relatively few instances has it been necessary to revoke licenses, although this has been done unhesitatingly when conditions demanded it.

The service to the public effected by this supervision of an important industry can be appreciated only by those who understand the conditions obtaining in this country before the passage of this act and those prevalent in countries where no such control is maintained. Under such conditions it is possible for preparations of known value at their best, such as diphtheria antitoxin, to be placed in the hands of physicians in such conditions of subpotency or of actual contamination as to be not only worthless but positively dangerous. Moreover, large numbers of valueless and even fantastic "cures" can be foisted upon the public.

DIPHTHERIA ANTITOXIN

One of the first acts of the Public Health Service in connection with biologics control was the establishment of an American standard of potency for diphtheria antitoxin. This involved, as may be understood, considerable original research in bacteriology and serology. A standard antitoxin was issued to manufacturers early in 1905 (Rosenau, HLB 21). Difficulties with this product have been few, but some of them have been serious. In 1909 unpleasantly severe local reactions were traced to a high concentration of total solids in the serum (AR *1909*, p. 21). The influence of age and temperature on the serum was studied by Anderson (HLB 66, *1910*). The Public Health Service brought considerable first-hand experience to bear on this product. Kinyoun had studied the preparation of antitoxin under Roux and observed its use at Koch's Institute in 1894. On his return to America he had produced and distributed the product at the Hygienic Laboratory, being probably the first to make and standardize antitoxin in the United States (AR *1904*, p. 412). Rosenau also was familiar with European practice in this particular.

The toxin-antitoxin mixtures used for immunization purposes were more troublesome than the antitoxin, and several unforeseen accidents occurred necessitating regulations for control. A comparison of results with toxin-antitoxin and those with toxoid was made by Harrison on over 700 children and was favorable to the latter as regards the establishment of Schick negativeness in the proportion of 95 to 64 (RPHR 1402, *1930*).

VACCINE VIRUS

Vaccine virus was another problem taken up early in the history of biologics control. At that time the average "take" following vaccination was likely to be a rather large and serious affair, which could be attributed, as we now know, to a combination of three factors: (1) The use of vaccine of high bacterial content purveyed on ivory points or insufficiently "ripened" in glycerin, (2) the practice of making unnecessarily large and deep scarifications, and (3) the practice of applying dressings to the vaccination site, which, aside from being entirely unnecessary, were often grotesquely unsuitable (bunion pads, for example) and led to serious and sometimes fatal complications. It is only fair to attribute the greater part of the enormous improvement in vaccination in this country to the unremitting efforts of the Public Health Service. Bacteriology, of course, has been the principal weapon in this fight.

In 1902 Rosenau had shown the high bacterial content of ivory points, as well as of unripened glycerin tubes (HLB 16), (AR *1902*, p. 440). With the passage of the biologics control act of that year the first factor mentioned above came directly under the control of the Government. The process of manufacture was so scrutinized and improved under bacteriological control that a steady decline in the bacterial content of vaccine was noted from the start, until an apparently irreducible average minimum was secured.

In 1908 there was a mild outbreak of foot and mouth disease among calves which had previously been used to propagate vaccine virus. Investigations were immediately begun by the Hygienic Laboratory, and an isolated building was constructed on the grounds in record time for study of the condition. The infection was found in the vaccine virus prepared from these calves. The licenses of two manufacturing firms were suspended and the product was condemned and destroyed. No human cases occurred during this period.

TETANUS FOLLOWING VACCINATION

Tetanus as a complication of vaccination, although very rare in proportion to the number of persons vaccinated, has occurred sufficiently frequently to require much study on the part of the Public Health Service. Anderson investigated two cases in 1909 but could find no tetanus organisms in the vaccine used. Eleven cases in 1912 were studied at the laboratory with the same result. Francis made a very extensive study of vaccine virus with reference to tetanus and found no instance of contamination. He condemned the use of vaccination shields (HLB 95, *1914*). In AR *1915*, p. 97, the statement was made that during the preceding 13 years enough vaccine to vaccinate 2,000,000 persons had been examined for the presence of tetanus contamination at the Hygienic Laboratory with entirely negative results. However, the presence of tetanus spores in materials used for dressings was established in commercial gelatin in 1902 (Anderson, HLB 9, *1902*), in court plaster (McCoy, Leake, and Corbett, RPHR 424, *1917*), and in bunion pads (Armstrong, RPHR 102, *1925*). With the latter study Armstrong began his investigation of vaccination sequelae, which has continued up to the time that this is being written.

In 1921 the Public Health Service adopted the rabbit method of testing the potency of vaccine virus (AR *1921*, p. 84) and during the same year recommended the use of minimal insertions and the abandonment of dressings of any sort other than a piece of sterile gauze pinned to the inside of the sleeve to absorb moisture. Direct dressings, even if sterile, were shown to promote swelling of the tissues and anaerobic conditions, and to hinder lymph drainage

(Armstrong, RPHR 1304, *1929*). Tetanus as a sequel to vaccination has decreased in frequency, yet such is the "cultural lag" among some physicians that nine cases of tetanus were reported in 1930, in seven of which shields or other dressings had been used. Data were not secured on the other two. As a result of the work of the Service in this connection it is known that one manufacturing firm voluntarily destroyed thousands of dollars worth of vaccine shields.

ENCEPHALITIS FOLLOWING VACCINATION

Post-vaccinal encephalitis is another occasional sequel to vaccination which has received much study at the Hygienic Laboratory. By 1931 the Service had collected reports of 85 proved or probable cases in the United States during the preceding 11 years. All attempts to reproduce the disease in animals at the Hygienic Laboratory with materials from cases following vaccination have failed. However, as an interesting side light, it may be mentioned that vaccine virus was recovered in a rabbit inoculated with spinal fluid from a human case of post-vaccinal encephalitis (Armstrong, RPHR 1309, *1929*).

Other work in connection with vaccine virus has consisted of the demonstration of cross immunity between smallpox and alastrim which had been considered by some a separate disease (Force and Leake, HLB 149, II, *1927*), (AR *1921*, p. 85), the isolation of a heat-resistant strain of virus by Armstrong (RPHR 1283, *1929*) by means of which it was possible to produce a vaccinal pneumonia in rabbits, a study of experimental vaccinia in rabbits (Lillie, NIHB 156, *1930*), and the interesting studies on the effect of certain substances when mixed with vaccine virus. For example, it was shown that diphtheria toxin when so mixed had the effect of reducing both the local and general response in rabbits, and that when previously administered in two doses to mice it afforded some resistance to intracerebral injections of vaccine virus. On the basis of these experiments it has been advised that children should be first immunized against diphtheria and about a month later vaccinated against smallpox (AR *1932*, p. 63).

ANTIMENINGITIS SERUM

Antimeningococcic serum has presented many difficulties of standardization which have been the subject of much study. The initial optimism regarding its effectiveness has been considerably abated by unfavorable results in many epidemics. Assuming that the product is really of considerable benefit when properly prepared, the question remains as to what criteria of excellence can be depended upon in testing various preparations. It is becoming better recognized

among bacteriologists that the mere presence of demonstrable antibodies in a given serum may afford no guarantee of preventive or therapeutic properties. Their presence, however, in considerable concentration in horse serum may be taken as evidence that the animal itself has been exposed to the corresponding antigens, and hence serves for the identification of the serum.

A great deal of research has been carried on at the Hygienic Laboratory regarding this question without, it is believed, a satisfactory answer having been secured. Early aspects of the problem are discussed by McCoy and Leake in RPHR 481, *1918*. Much of this work is unpublished. Grouping tests of meningococci were made in 1920 (HLB 124). One obvious difficulty lies in the unheralded appearance in epidemics of new strains of meningococci against which the current sera may not be effective. Dr. Evans had shown in 1922 that a marked shifting of prevailing types had occurred since former years. Out of some 75 strains collected during the Chicago epidemic of 1928, 26 were found by Dr. Branham to represent an entirely new form to which the name *Neisseria flavescens* was given (RPHR 1368, *1930*). Some of the firms hastened to include this strain in the preparation of serum, but up to the time of this writing no recurrence of this organism in epidemics has been observed. In 1931 the examination of 320 strains of meningococci had been completed by Dr. Branham and her associates, 82 percent of which were found to fall into groups I and III of Gordon's classification. The generalization was arrived at that all meningococci ferment both glucose and maltose, thus affording a secure basis of differentiation from the gonococcus (RPHR 1469, *1931*). Since then the study of strains has extended to nearly a thousand, with only some half dozen exceptions (and those incompletely determined) to this rule. Newer phases of this work are the suitability of mouse protection tests and the possibilities of antitoxins produced against a soluble toxin of the organism. The difficulties of this type of work are that one cannot wait for the performance of a given serum during an epidemic to furnish a criterion as to its potency (and even then the next epidemic might reverse the evidence), but must pass upon the issue of preparations in advance. While it is known that the soluble toxin is capable of causing a definite meningitis in mice by cisternal administration, the antitoxin cannot be administered in this way to determine its potency because horse serum is very toxic of itself. Factors complicating the employment of the Shwartzman phenomenon in testing antimeningococcic serums are discussed by Pabst and Branham in RPHR 1579, *1933*. The mouse protection test is discussed by Branham in RPHR 1689, *1933*.

SCARLET FEVER SERUM

With the advent of the experimental use of a streptococcus serum in the treatment of scarlatina, and the application by firms for licenses for the product, the problem of devising methods for its control came before the Public Health Service as an imperative and nondelegable duty. After prolonged studies at the Hygienic Laboratory, Dr. R. E. Dyer devised a test for this product in which skin tests on human beings were employed (RPHR 998, *1925*, and 1007, *1925*). In the same year firms were licensed for toxin production, and in the following year tentative scarlet fever antitoxin standards were distributed (AR *1926*, p. 64). It was not until 1928, however, that a standard unit of scarlet fever antitoxin was promulgated. This was based on the minimum amount of toxin necessary to cause skin reactions in the majority of nonimmune persons. Five times this amount constituted a test dose of toxin, and the unit of antitoxin was 10 times the amount necessary to neutralize a test dose. By this arrangement the dosage of serum in units was brought approximately to that of diphtheria antitoxin, thus relieving the physician of the necessity for remembering differences, and in the long run, undoubtedly avoiding unpleasant mistakes (Dyer, RPHR 1234, *1928*). The efficacy of this serum in the treatment of scarlet fever was reviewed by Veldee and others in 1931 (RPHR 1519), and in the next year Veldee published a method of standardization in which the ears of white rabbits could be substituted for the human skin (RPHR 1533).

While there is no doubt that children may be immunized against scarlet fever by injections of toxin, the high hopes of securing a widespread immunity in this way, comparable to that obtained in the case of diphtheria, have been considerably dashed by the occurrence of severe reactions. Veldee sought to avoid this difficulty by producing a toxoid which would give milder reactions (RPHR 1574, *1933*). He did, in fact, avoid this difficulty, and succeeded in rendering some 60 percent of children nonreactive by a single injection of the toxoid. An objection was found to the product, however, owing to the high protein content of the preparation. Another approach to the problem is therefore being pursued. Early studies of streptococci and their serums, by Evans and by Enlows, are found in HLB 134, *1923*.

ANTITETANUS SERUM

Antitetanic serum required for its standardization researches similar to those employed in the case of the diphtheria product. Again it is interesting to note that Kinyoun had observed the methods of Behring and Kitasato in Berlin in 1891. When, in 1907, the Hygienic

Laboratory took up the question of standardization under the Biologics Act, the greatest diversity among current preparations was discovered. When compared to a common standard the extreme variations encountered among seven samples were from one claiming 6,000,000 units and containing 90, to another claiming 0.75 units and containing 769. No better argument for central control could be offered. The standard tetanus serum unit was promulgated in 1908 (HLB 43).

Since the Public Health Service now issues licenses to some 49 manufacturing firms, covering approximately 155 different biological products, and since every one of these products is subjected to periodical bacteriological or serological tests, and since many products have necessitated some, or even very extended, research before methods for control could be devised, it is evident that this chapter would become interminable if every product were considered at length. For this reason reference will be made to only a few remaining products.

Botulinus serums A and B were standardized in 1920. Early samples submitted for test varied in unit content from 2 to 450 per cc. Further studies of the organisms concerned were made by Bengtson in 1924 (HLB 136). She had described a direct inoculation test for the presence of toxin in 1921 (RPHR 677). Serums against the gas gangrene organisms (*perfringens*, *Vibrion septique*) were among the latest to be standardized (RPHR 1617, *1934*), (RPHR 1624, *1934*), (RPHR 1664, *1934*). Dr. Bengtson performed this difficult and exacting work.

UNCONFIRMED "CURES"

Not the least of the public services rendered by this activity has been the prevention of exploitation of the public by "cures" for which licenses were desired or demanded, but which on actual test could not reproduce the claims of their supporters. A tribute is due to Dr. McCoy as director of the laboratory for his patient, fair-minded, and sagacious handling of these cases. Cures for tuberculosis have easily headed the list of these preparations. In several instances where the claimants have been apparently sincere and possessed of at least fair scientific competence, they have been invited to come to the Hygienic Laboratory and demonstrate their methods. In most of these cases the claims had been made that experimental animals could be protected against or cured of tuberculous infections, and the whole argument was allowed to rest on the outcome of animal tests. Since these attempts always turned out negatively, the claimant left without the license, and, it is believed, without ill will.

In another category were the claims of Friedmann and of von Ruck. These were based upon the effects on human subjects only, although in the latter case serological tests were taken as evidence of improve-

ment or recovery. The furore created by Friedmann's sensational visit to this country was comparable to that produced by Koch's original and disastrous employment of tuberculin in Berlin in 1891, as described by Dr. Kinyoun of the Public Health Service. In fact his comments, with slight modifications, seem sufficiently applicable to the Friedmann episode to bear repetition. Kinyoun found Berlin crowded with physicians and patients interested in the tuberculin treatment. In his own words,

> Berlin had momentarily become a great hospital. tuberculous patients were everywhere, and generally speaking, in the last stages of the disease. * * * At this time Professor Koch had not intimated a word concerning the composition of this substance, or the manner of its preparation. It was evident from the first that the peculiar substance was capable of doing great harm as well as good. (AR *1891*, p. 57–62.)

The modifications which we would make in applying Kinyoun's statements to the Friedmann case are the substitution of New York for Berlin, Friedmann for Koch, and omitting reference to the good results. That there were cases of apparent improvement is true, but a checkup after a year on the treated and untreated control groups showed no significant differences. In joint cases with secondary infections and sinuses, initial improvement sometimes followed the intravenous injections of the material, apparently as a result of nonspecific protein reactions; but this proved to be only temporary, or, if more permanent, it was then matched by similar improvement in untreated cases.

Anderson and Stimson represented the Public Health Service in this investigation. License for the product was refused (HLB 99, *1914*). The von Ruck investigation was undertaken as a result of a Senate resolution (which the Drs. von Ruck induced an influential member to secure). Here the question of license was not involved, since the products put out by the von Ruck laboratories were already licensed along with a number of preparations by other firms having the general nature of tuberculins. What was sought was an official endorsement by the Service for the von Ruck methods of treatment, it being claimed that they represented a marked advance over current methods in the therapy of tuberculosis. The criteria were to be the clinical improvement of treated cases, and more particularly a series of serological manifestations which were claimed to be indices of improvement or cure. An independent investigation was conducted simultaneously by the United States Navy Medical Corps. Dr. George Crow represented the Navy and Dr. Stimson the Public Health Service. The two reports were in agreement and to the effect that the theoretical structure of the method was invalidated by the inadequacy, to say the least, of the technique. Opportunities for impartial clinical observations were not afforded. En-

dorsement of the method was therefore withheld (AR *1915*, p. 86) (Sen. Doc. 641, 63rd Cong.).

ANTISYPHILITIC ARSENICALS

Shortly after the introduction of salvarsan by Ehrlich in Europe, samples were secured by the Public Health Service for experimental use, and selected cases submitted by practicing physicians were injected by Service personnel, these being among the first to be treated in this manner in this country. The marvelous initial results were observed and their public health significance was appreciated; but, at the same time, the danger to the public of permitting the uncontrolled distribution of such potent remedies was recognized. Under a Treasury Department ruling the new arsenical drugs intended for the treatment of syphilis were brought under the Biologics Act, for, while obviously not of biologic origin, the dangers to life, the care necessary in preparation, susceptibility to deterioration and contamination, and the parenteral method of administration brought them into the same category as regards the public health. This control brought with it many problems of chemistry, pharmacology, and chemotherapy, and there have been many contributions by the Service in this connection; but since these rather remotely affect the subject of bacteriology, further discussion will be omitted.

BRUCELLOSIS

Not until about 1927 did brucellosis, more commonly known as undulant fever, become recognized in the United States as a public health problem of considerable though not major importance. According to reports collected by the Public Health Service from year to year, the prevalence has been as follows: 1927, 114 cases; 1928, 669 cases; 1929, 975 cases; 1930, 1,453 cases; 1931, 1,578 cases; 1932, 1,502 cases; 1933, 1,788 cases; 1934, 2,017 cases; 1935, 2,008 cases; 1936, 2,095 cases; 1937, 2,458 cases. There can be little doubt that the apparent increase is due chiefly to increasing recognition and better reporting, since other circumstances, principally the increasing extension of milk pasteurization, lead to the belief that the actual trend has been in the opposite direction. It cannot be considered that even the maximum figures given here represent nearly all of the actual cases. The disease is so insidious, indefinite in symptomatology, and so easily confused clinically with other infections that, without laboratory assistance, a correct diagnosis must frequently be missed. Hasseltine pointed out the confusion which might arise in cases of suspected but unproved tuberculosis (AR *1932*, p. 60), which may occur also with regard to enteric, rheumatic, and other infections, and indeed noninfectious clinical conditions.

The first case in which the disease was brought directly to the attention of the Public Health Service was in that form which has later proved to be the least important in this country, the old Malta fever derived directly from goats or from goats' milk. In 1922, G. C. Lake investigated an outbreak, the first in this country of sufficient proportions to be called an epidemic, at Phoenix, Ariz. There were some thirty-odd cases, and the infection was readily traced to a herd of goats. Examination of human and goat serum at the Hygienic Laboratory confirmed the diagnosis and indicated a prevalence of 18.3 percent among 115 goats tested. Lake recommended the pasteurization of the milk, which had been consumed raw, and the epidemic subsided.

In 1918 Alice C. Evans had shown the close resemblance of the *melitensis* and *abortus* organisms. Following her transfer to the Public Health Service she continued her studies on these bacteria and published a number of short papers on questions of classification and nomenclature, on the infection of a cow with a human strain of *Br. melitensis*, on cattle as a source of human infection, and on hogs as a possible source. The substance of these papers is brought together in HLB 143, *1925*. The basis of classification of the large number of strains of various origins which she studied was the agglutinin absorption test. However, Francis (RPHR 1513, *1932*) showed the discrepancies between determinations made by this method and those made by Huddleson by his bacteriostatic dye methods; and, furthermore, taking the CO_2 requirements of the *abortus* organism as a criterion, he found that certain strains thus established as the Bang organism nevertheless by absorption tests appeared to be *melitensis*. He concluded that the agglutinin absorption test was not a reliable method of classification, although conceding that the results of agglutination by serums previously cross-absorbed might be useful as presumptive evidence. He described convenient methods of adding measured amounts of CO_2 to jars used in cultivation of these bacteria.

The Public Health Service has made a considerable number of contributions to the epidemiology of brucellosis and has been instrumental, through its direct appeals to health officials, in securing its recognition as a largely preventable hazard of considerable importance. Thus, Hardy (RPHR 1212, *1928*) showed that numerous cases could be brought to light merely by adding *Brucella* agglutination tests to the Widal tests on serums sent in to health laboratories. The cases thus brought under suspicion were then investigated individually from an epidemiological standpoint. He advanced the hypothesis that, in view of the widespread contamination of milk and its consumption in a raw state, the relatively infrequently recognized infection of man was due to a rather preva-

lent childhood infection with subsequent immunity, infections in children being relatively mild and likely to escape recognition (RPHR 1247, *1928*). Hasseltine, with G. E. Atwood, a county health officer in Georgia, studied a small but clean-cut outbreak, and found that in a city of 23,000 where raw milk and pasteurized milk were used in about equal amounts, all of the nine cases in the outbreak were users of raw milk. The dairy sources were known to have reacting cows. The porcine strain was implicated. With the increase of pasteurization to about 90 percent, new human cases failed to appear (RPHR 1383, *1930*). Hasseltine, in a study of Hardy's and his own collected data (RPHR 1395, *1930*), found that 198 cases were probably infected by dairy products, 44 cases by contact with hog carcasses, while in 200 cases exposure had been both to infected livestock and dairy products.

These combined studies have led to the conception that man may become infected with any of the strains from the three principal animal sources, caprine, bovine, or porcine, though not necessarily from the animal indicated, since these strains are not host specific; that cases are about equally divided between those which receive their infection from milk and other dairy products, and those acquiring it from contact with infected animals or their slaughtered carcasses; that for the former group efficient pasteurization is the only reliable preventive, while for the latter, individual vigilance and precautions will have to be relied upon pending the slow process of eradication of the infection from herds.

The strong penetrative properties of these organisms have been repeatedly shown on animals and unfortunately demonstrated in a high percentage of laboratory workers. The organism will infect through the unbroken skin and conjunctiva, and infection in the laboratory is believed to occur principally during the handling of animals and the use of living or incompletely sterilized antigens.

CHOLERA

The Hygienic Laboratory was established during the year following Koch's announcement of the discovery of the *Vibrio cholerae* (1886). During its first year it bacteriologically demonstrated cholera on steamships entering New York harbor (AR *1888*). In 1894 a death occurred in Cumberland, Md., in a recently arrived immigrant from Bremen. Cholera was suspected, but Dr. Geddings, who was sent to investigate, was unable to recover the organisms from the exhumed body (AR *1894*, p. 280). In 1895 Sanitary Inspector Ryder reported cholera in Honolulu, made cultures, and sent in stained slides of the organism (AR *1895*). Perry reported an epidemic in the Philippines and gave some historical data in AR *1903*.

In 1911, when cholera arrived again at the port of New York, combined city, State, and Public Health Service forces made bacterial examinations of the feces of all arrivals from infected areas, discovered 26 carriers, and recorded 35 cases, of which 20 died. In spite of these precautions some infected persons apparently were landed, since 4 cases, 3 of them fatal, were detected in New York and its vicinity at that time. Although the bacteriological methods then used were reasonably effective, improvements were sought and several were suggested by Public Health Service workers (RPHR 52, *1910*), (RPHR 53, *1910*), (HLB 91, *1913*), and the adaptation of cholera media to post-war peptones by adjustment to pH 7.2 was achieved (HLB 139, *1924*).

Although cholera has ceased to be a matter of concern in the continental United States, owing chiefly to the improvements in public water supplies, it occasionally assumes serious prevalence in the insular possessions. The National Institute of Health maintains a supply of high titer serum for diagnostic use in emergencies.

DIPHTHERIA

Most of the contributions of the Public Health Service in connection with diphtheria have centered around biological products (see p. 16) for its prevention or treatment. While the statistical reports of the Service abound with evidences of the progressive control of mortality by the use of antitoxin, and of morbidity by the use of toxin-antitoxin and toxoid, contributions of purely bacteriological interest are relatively few. Among these may be mentioned the early inquiry into the nature of diphtheritic paralysis (HLB 38, *1907*), and the investigation of the carrier problem by Goldberger and others (HLB 101, *1914*). It is believed that attention was first called to the toxic gastric ulcers of guinea pigs by Service workers (HLB 32, *1906*).

DISINFECTANTS

Because of the nature of its work, especially during the period when bacteriology was first applied to public health practice, the Service needed to know about disinfectants, and it sought this information largely at first hand. The earliest applications demanding attention were those of gaseous disinfectants for ships, in connection with the quarantine duties of the Service. Thus, as early as 1889 we find the infant Hygienic Laboratory making bactericidal experiments with various gases esteemed at that time in various quarters as disinfectants, including bromine, chlorine, phosphorus pentoxide, nitrous oxide, and sulfur dioxide, and finding the last the most penetrating and efficient, although it would not kill spores. By 1896 interest had shifted largely to formaldehyde gas, and a number of

reports of its experimental use appeared in Service publications of that period. Since, however, there was a pressing demand for insecticides on ships, especially against mosquitoes in connection with yellow fever, further studies were made which showed the superiority of SO_2 gas over formaldehyde for this purpose (HLB 6, *1901*). The necessity for the control of humidity and temperature in gaseous disinfection with formaldehyde and its consequent practical limitations were brought out by McClintic in 1906 (HLB 27, *1907*). In another connection, the preservation of biological products, Anderson studied the bactericidal properties of formaldehyde solutions (HLB 39, *1907*).

The shift of public health emphasis from terminal gaseous disinfection in the direction of concurrent bedside disinfection led to the introduction of a great many commercial preparations for which certain advantages were claimed. It was really a matter of great public health concern that these products should be effective, especially in the case of diseases like typhoid fever where spread through the excreta was a common experience. Although the Service was not directly vested with control powers, it was utilized as a testing agency by the Insecticide and Fungicide Board, and standard methods of testing disinfectants were developed at the Hygienic Laboratory in 1911. These methods and the results of applying them to a variety of commercial disinfectants were described by McClintic in HLB 82, *1912*. The method was admittedly difficult and painstaking and required considerable training of a technician before it could be employed successfully. Nevertheless it was found to give more trustworthy results than a number of short-cut substitutes which were proposed. Much of the onerous work of employing it was obviated by a testing machine developed at the laboratory by Stimson and Neill (RPHR 462, *1918*). In 1921 a modified method of testing disinfectants was published in RPHR 675. In later years this activity was turned over to the Government agency empowered with legal control over these substances.

In recent years the problems of ship disinfection have been concerned, in general, with the destruction of rodent and insect vectors, more specifically rats and mosquitoes. Even airplanes are now routinely disinfected by the Public Health Service at some quarantine stations, since potential yellow fever infection is now distant by only a matter of hours instead of days. In the case of ships, cyanogen is immeasurably superior to other known fumigants on account of its penetrating qualities and its prompt lethality to both rodents and insects. Its use, however, unless stringent precautions are employed, is dangerous to human life. The earlier precautions consisted of a rigid discipline and method practiced by trained personnel. involving the clearing of the vessel of human beings, accurate timing

of procedures, proper ventilation, and the use of gas masks. In spite of these precautions, occasionally a stowaway somewhere among the lading was killed. The use of warning agents such as chlorine has in some instances saved life, but it introduces some dangers of its own. The subject of fumigation is thoroughly discussed by C. L. Williams, whose scientific and practical knowledge makes him a dependable authority (RPHR 1763, *1932*). Earlier contributions to this subject were made by Creel, and by Faget, of the Service (RPHR 313, *1915*), (RPHR 343, *1916*). A method for the office disinfection of dental instruments was devised by Hasseltine (HLB 101, *1915*), and a description of the practical use of disinfectants in general health work by the same author is found in RPHR 287, *1915*.

At that time there was much agitation among undertakers to secure a generally recognized embalming procedure applicable in cases of death from any cause, and one which would facilitate the transshipment of corpses across State borders without delay. Owing to the varying regulations of different States, most embarrassing and even distressing incidents had occurred. The task of devising such a method was given to Francis, whose satisfactory solution is reported in RPHR 292, *1915*. It was during the human phase of these experiments that one of the stock traditional stories of the Hygienic Laboratory arose. A Negro coal deliveryman, in searching for the coal bin the basement, by mistake opened the door to the room in which an embalmed corpse of the same race, somewhat distended by copious injections, was undergoing the high temperature test of efficiency. It is related that his exit from the building was observable only as a dark streak accompanied by a gale of wind; and considering the observed initial velocity, it is believed that he must still be "going strong."

ENCEPHALITIS

Post-vaccinal encephalitis has been referred to under "Biologic products." Epidemic encephalitis, or encephalitis lethargica as it was formerly known, appears to have been first established as an entity by v. Economo in Vienna in 1917. In the United States cases were reported from widely separated localities in the form of small epidemics. H. F. Smith of the Public Health Service collected reports of 255 cases between September 1918 and May 1919. He personally examined 178 of these and secured data altogether on 222. His clinical and epidemiological study of these records constitutes the first scientific contribution to the subject by the Service (RPHR 641, *1921*). In following years morbid material from cases was studied at the Hygienic Laboratory with inconclusive results, and it was not until 1933 that the fact of the transmissibility of the dis-

ease to monkeys was established. In that year, with materials secured from the St. Louis epidemic, Armstrong of the Public Health Service, working with Muckenfuss and McCordock of Washington University, succeeded in establishing the infection in *Macacus rhesus* monkeys and in white mice by subdural inoculation of brains and emulsions. *Cebus* and Java monkeys appeared to be refractory, as were rabbits. Experimental animals thus became available to future investigators (RPHR 1600, *1933*).

As a result of the studies of Leake and those of others, of the epidemiology of encephalitis in general and of the 1933 St. Louis epidemic in particular (Am. J. Pub. Health, *1933*, **23**: 1135, 1140, 1144, 1148), and of laboratory studies of viruses obtained during the epidemic, it became evident that a distinction must be made between encephalitis lethargica and the recently investigated forms, to which the name "epidemic encephalitis" was given. It appears from a study of the literature that there are probably a number of similar but distinct infections of this nature, as there are in the typhus fever group. In the immunological field, workers outside the Service had shown the feasibility of mouse protection tests (Webster and Fite), and these were now employed by Wooley and Armstrong in a miscellaneous population as regards previous infection, to determine if possible the antecedent distribution of infections. Widely separated parts of the country were represented and 524 sera were examined. In a group known to have had the St. Louis infection, 94.8 percent of the sera were found to give positive mouse protection tests, while in a group giving no history of any infection of this nature, 9.7 percent were found also to give positive reactions. In view of the apparent specificity of this test against lethargic and post-infectious encephalitis and poliomyelitis, the authors attribute these findings to a fairly widespread prevalence of unrecognized infections with epidemic encephalitis of the St. Louis type (RPHR 1662, *1934*). Armstrong also showed that the immunity acquired by white mice which recovered after intranasal inoculations with the St. Louis virus was specific (PHR *1934*, p. 959).

LYMPHOCYTIC CHORIOMENINGITIS

A significant byproduct of these virus studies was the definite establishment of a new disease of man. Vietts and Watts, and Dickens, independently of the Public Health Service, had described cases of encephalopathy differing from encephalitis of known origins and characterized by preponderance of lymphocytes in the spinal fluid. Since these were accompanied by no observable bacterial infection, they were described as aseptic meningitis. From the laboratory approach Armstrong and Lillie (PHR *1934*, p. 1019) had

isolated a virus giving a clinical and pathological picture entirely different from that of encephalitis virus. Although coming from a monkey in a series originally inoculated from a human case of supposed encephalitis, it appeared only after six passages, and its origin was therefore obscure. This origin is discussed in a paper (PHR *1935*, p. 537) by Armstrong and Wooley in which three strains are described, two of which were possibly of human origin. However, one was definitely of monkey origin, and the sera of some uninoculated monkeys were found to be protective, as were some human sera. Further light on this interesting infection, for which the more suitable name of "lymphocytic choriomeningitis" was proposed, is given in the article by Armstrong, and Dickens of the United States Navy, in which additional human cases are reported, the clinical picture in human beings and monkeys is described, and the protective properties of serum from recovered cases is further established (RPHR 1691, *1935*). Bengtson and Wooley cultivated this virus in chick embryos (PHR *1936*, p. 29), and the pathology of these embryos has been described by Lillie (ibid, p. 41), and the latter author has described the pathologic histology in monkeys (PHR *1936*, p. 303). The distribution of the virus in monkey organs is discussed by Armstrong in PHR *1936*, p. 296.

It is by means of such contributions as the above that the puzzle picture of the virus diseases is gradually being put together. The occurrence of latent virus infections in experimental animals is now well known, the above being one example of them. Can we infer a similar condition in human beings, in which various slumbering infections of this nature await only some stress or an intercurrent infection to arouse them to a virulence sufficient perhaps to become the starting point of an epidemic? Again, is the continued state of immunity evidenced by serological reactions only an index of the residence of living organisms within the body? The rational public health control of this class of diseases must await the solution of these and similar questions, unless some practical short-cut can be devised. Such a procedure, for example, as the nasal instillation of protective chemicals as practiced so successfully on an experimental scale by Armstrong and Harrison might relegate questions like the above to the academic field (PHR *1936*, p. 203). A preliminary field trial has indicated that there are technical difficulties still to be overcome.

GENERAL BACTERIOLOGY

It has been difficult to make a selection of contributions to be included under this heading for the reason that one never knows just what will prove to be important as the years pass and knowledge increases, and yet selection must be made from the hundreds of iso-

lated observations which are not readily classifiable under any other caption convenient for the present purposes.

The studies of oxidation-reduction phenomena conducted for several years at the Hygienic Laboratory by William M. Clark and his associates would seem to have inevitable significance with regard to the future development of bacteriology, although few of them have dealt directly with that subject. Clark's contributions to the subject of hydrogen-ion concentration have had such widespread influence on the pursuit of a wide variety of public health laboratory conceptions and techniques that much may be expected from his development of this other universal biological subject. Ten of these studies are collected in HLB 151, *1928*, and subsequent contributions are found in SPHR 69, *1928*; 71, *1928*; 74, *1928*; and 92, *1931*.

In the same way the researches of Hudson and his coworkers at the National Institute of Health on sugars and enzymes can confidently be expected to yield information of great value to bacteriology. Many of the sugars used in fermentation tests in the past have undoubtedly been impure, and much of the discrepancy in determinations by different observers may be attributable to this. As knowledge of the constitution of sugars increases, and as better methods for their preparation in a pure state become developed, we may expect to see some obscure points in bacteriology cleared up.

In the field of immunity the work of Armstrong and Harrison on a species of nonspecific immunity which they designate "heterologous experience" may prove to have far-reaching significance. Acting on various observations in the literature to the effect that recovery from one disease might increase the resistance of a person to other and apparently unrelated diseases, they tested out the theory on animals with quite suggestive results. For example, they found that in guinea pigs previous exposure to various combinations of tetanus toxin, botulinus toxin, and vaccinia, in sublethal doses, gave 38.4 percent of survival in a series of animals subjected to marginal doses of diphtheria TAT mixture, while the control series had only 11.4 percent of survival. In monkeys treated with diphtheria toxoid the survivals following poliomyelitis inoculations were 17.8 percent as compared with 11.5 percent in controls. In a series receiving preliminary treatment with typhoid culture, and injections of *B. prodigiosus* as the test organism, 28.6 percent treated intraperitoneally and 33.3 percent treated subcutaneously survived, while only 7.7 percent of the untreated animals lived (RPHR 1576, *1933*).

The work of Armstrong in the protection of animals against poliomyelitis inoculations by nasal instillations of various chemicals has been referred to elsewhere, but is again mentioned because of its possible general applications.

In the field of bacteriological technique, Spencer's observations on the apparently specific clarifying effect of soap solutions (sodium ricinoleate) on cultures of *B. tularense* and some other organisms, may prove of practical and theoretical importance (RPHR 1658, *1933*), while his device for preventing aerial contamination in the handling of cultures will doubtless be useful in many research connections (RPHR 1719, *1936*).

The employment of Barber's single cell isolation technique in the hands of Dr. Bengtson has led to some discoveries of general bacteriological significance. In the process of obtaining a pure culture of an anaerobe which she later proved to be a new type of the botulinus organism (type C), Barber's techinque was employed. From a culture arising from a single colony of a toxic growth of this organism, three single cells were isolated which gave rise to two nontoxic and one toxic culture. Further single cell transplants from these cultures established the principle that some of the progeny of a single bacterium may resemble the parent in possessing the property of producing powerful toxins, while others may be entirely lacking in that property. The progeny of nontoxin-producing cells, however, never in her experience gave rise to toxin-producing progeny (RPHR 785, *1922*) (HLB 136, *1924*). Toxin production would therefore appear to be a recessive quality. Similar facts have since been demonstrated with reference to other bacteria, but usually in association with certain cultural differences in the cultural characteristics, such as rough and smooth colonies. Dr. Bengtson, on the other hand, could not discover any differences in the progeny strains except with regard to toxin production.

INFECTIOUS JAUNDICE

It is probable that this disease is not as rare in the United States as the reported figures indicate. The close resemblance of mild cases to catarrhal jaundice may readily permit its nonrecognition. Some students believe that outbreaks of jaundice during the Civil War, and even during the War of 1812, were due to this disease.

Wasdin reported to the Service two cases in Buffalo in 1903 (AR *1903*, p. 354). In 1918 Neill made some investigation of the prevalence of the disease and listed 19 American outbreaks. He studied the prevalence among wild rats of Washington, D. C., and found about 10 percent of them harboring *Spirochaeta icterohemorrhagiae* (as then named), which figure corresponded roughly to those of investigators elsewhere (PHR 466, *1918*).

Ridlon made a similar survey in San Francisco in 1931, using the technique of dark-field examination of macerated kidneys, and found a much higher percentage by this perhaps not very searching method—17 positive for the leptospira out of 50 specimens (RPHR 1439, *1931*).

Since there appears to be no dearth of rat infestation with this parasite (which apparently does not cause illness among them), human infection is apparently dependent upon some unusual set of circumstances of intimacy with the rat population, such, for example, as military service in trenches. It is something to be borne in mind in cases of unusual prevalence of jaundice.

The probability that the parasite had first been seen in tissues from a case of supposed yellow fever is referred to in the chapter on that disease.

INFLUENZA

The studies on influenza by the Public Health Service have been very numerous, continued over a long period of time, and in the aggregate constitute valuable contributions to the history of the subject. Since the attempts to transfer the infection, to secure an experimental animal, discover the etiological agent, and establish a specific preventive, have all been unsuccessful, the investigations and their records would be of interest only to the special student. It now seems apparent that the solution of these problems was dependent upon the development of a new technique, the ferret-virus procedure.

It is believed that the contributions of the Service to the epidemiology of influenza will be appreciated more and more as time goes on, when future epidemics occur and the need for a large volume of data, carefully collected and analyzed, becomes apparent. One question which will almost certainly arise is whether these new outbreaks are of identical nature with those which have occurred in the past. When the great epidemic of 1918–19 occurred there were no records of such magnitude and dependability for reference. That epidemic and succeeding ones have been carefully recorded by the Service. Since, however, these studies belong to the subject of epidemiology rather than to bacteriology, no specific reference to them will be made here.

LEPROSY

In 1899 an act of Congress imposed upon the Public Health Service (then the Marine Hospital Service) the duty of appointing a commission of medical officers to investigate the origin and prevalence of leprosy in the United States. In succeeding years the leprosy problem in the continental United States became fairly accurately delimited, and agitation was begun for the establishment of a national leprosarium under its management. These plans did not mature until 1921, when the Carville Leprosarium was purchased from the State of Louisiana. All of the States are authorized to send their lepers to this institution, a model of its kind, where some 400 patients are constantly in residence. It appears to be the aim of this institution,

quite aside from specific therapy, to give its inmates the best chance for recovery by the medical and surgical treatment of all discoverable defects and morbid conditions, an enlightened policy not perhaps universally employed. Among its research contributions, not all of which are of immediate bacteriological interest, may be mentioned the curious modifying reaction between leprosy and vaccina. Not only were vaccinial lesions more severe in these patients than in non-leprous controls, but there was lighting up of the leprous process locally and in areas remote from the vaccination, at times with fever resembling "leprous fever." Moreover, there was noted an apparent increase of the numbers of Hansen bacilli in the involved tissues (Denny and Hopkins, RPHR 805, *1923*). Hasseltine confirmed many of these observations in Honolulu, and he attributes a popular native tradition that vaccination caused leprosy to the possible lighting up of subclinical cases by vaccination (RPHR 808, *1923*). One cannot avoid the impression that hidden in these phenomena there may reside some very significant principles of immunology. A study of the treatment of 44 patients with mercurochrome apparently showed definite improvement in 36 percent (RPHR 1036, *1925*).

The Public Health Service has conducted researches upon leprosy in the Hawaiian Islands since 1909, when an investigation station was opened at Kalawao on Molokai. Most of the studies, however, have emanated from the Kalihi station in Honolulu, where conditions for research are more favorable. There have been perhaps 50 or more contributions from this source in Service publications since this station was established, but it would seem that a thorough documentation of them is not called for in this place. They have dealt with many phases of the problem—epidemiological, bacteriological, and immunological. While none of them has been epoch-making (indeed what has been in this connection since the discovery of the bacillus?), they have built up a solid basis for the practical handling of leprosy. One important effect of these activities is that patients, even among unenlightened natives, have been attracted to institutional care rather than, as was formerly the case, encouraged to attempt concealment. The problem of control in a relatively highly infected population has therefore been made easier.

Many of these studies concern the treatment with chaulmoogra oil and its derivatives. Early experience, as in the case of so many new therapeutic agents, appeared highly favorable, so much so in fact that it appeared to be a duty to treat all patients in this way. It was only after the experience of years began to show an unexpectedly high relapse rate among paroled patients that doubts of efficacy became sufficiently strong to lead to comparisons with control treatments. Now, after some 15 years of experience, it is believed that little confidence is placed in the specificity of these preparations.

Neill, in 1924, referred to the rather unsatisfactory results from the ethyl esters of chaulmoogra oil, while Wayson, in 1929, after comparative tests, could see no advantage of this treatment over merely a good diet supplemented with cod-liver oil. He discovered a high prevalence of glycosuria among his patients (23 percent) as compared with a control group (3 percent) and noted considerable general improvement after installing a reduced carbohydrate diet.

Naturally many attempts have been made at Kalihi, as elsewhere, to cultivate the lepra bacillus. In some instances acid-fast organisms have been cultivated from leprous tissue, but proofs of their identity have not been forthcoming. The last and most pretentious of these attempts, completed in 1932, involved 40 types of media, both aerobic and anaerobic techniques, and partial pressures of CO_2 gas. In only one instance was an acid-fast organism cultivated, an orange pigment producer which was capable of inducing ulcerating nodules in animals. The tissue culture method was successful to the extent of reproducing an apparently proliferating acid-fast organism through 15 transfers (AR *1932*, p. 28).

The high incidence of positive Wassermann reactions in leprosy has long been noted at Kalihi. This is apparently not attributable to a complication with syphilis (Badger, RPHR 1471, *1931*). The relation between leprosy and tuberculosis also has long been studied. In 1914 it was pointed out that necrosis of lymph glands in leprosy was nearly always due to tuberculosis, and a warning was given against confusing tubercle bacilli with lepra bacilli in animal experiments.

Rat leprosy has been under study at Kalihi and elsewhere for over 15 years. Although not believed to be identical with the human disease, it has been hoped that something might be learned from it by analogy. The most interesting feature of this work of recent development is the fact that rats placed on a diet deficient in vitamin B_1 exhibit a reduced incubation period after inoculation with rat leprosy materials, and a heightened susceptibility to inoculations with human leprosy suspensions (Badger and Sebrell, RPHR 1692, *1935*). That rats could harbor human lepra bacilli in their tissues, even after intranasal inoculation with the latter, has been reported (AR *1931*, p. 35).

The history of leprosy and its study in Hawaii has been very entertainingly reviewed by Binford (PHR *1936*, p. 415).

MEASLES

Aside from statistical and epidemiological studies of measles, the chief contribution which the Public Health Service has made to the knowledge of this disease consists of a series of experiments on trans-

mission to monkeys performed by Anderson and Goldberger (PHR *1911*, pp. 847, 887) (RPHR 62, *1911*) (J. A. M. A. *1911*, 57: 113, 478, 971, 1612). These experiments provided medical science with an experimental animal, though, as the authors point out, not one of high susceptibility, at least by the methods of inoculation which they employed. Some of the filtration experiments were successful, which would indicate that the organism belongs in the group of filterable viruses, and is at variance with various claims to the bacterial and especially the streptococcic origin of the disease. However, the last word has not been said on the subject of the relation of filterable forms to bacteria which may be biologically related to them, nor on the subject of the symbiosis of unrelated forms in the etiology of disease. The successful transfer by means of blood and nasal and buccal secretions, and the unsuccessful attempts with scales from the skin, lead to the inference that the latter are not infectious and that the systems of isolation and quarantine based upon supposed danger from this source were not well founded. Infectivity of secretions appeared to be greatest immediately before and for a short time after the appearance of the exanthem. It is believed that where public health procedures have been modified in accordance with the indications of these experiments a considerable saving of effective school time has been realized, without any increased danger to the public.

MILK

The public health aspects of milk have received a great deal of study in the Public Health Service. Long before the publication of the Milk Bulletin (HLB 41, *1908*, revised and enlarged as HLB 56, *1909*), Service officers were interested in the subject in both its laboratory and administrative phases. In this bulletin of over 800 pages, however, this interest was emphatically registered and significant studies were reported. At the same period the studies of typhoid fever in the District of Columbia (see p. 65), were under way, and they served only to intensify the appreciation of the importance of milk as a vector of disease. In the same year (1908) Rosenau made a study of the thermal death points of pathogens in milk (HLB 42). At that time market milk in the United States, while a step in advance of what it was in some European countries, fell far below adequate health standards. While standards had been set up, they often missed the essentials, and they varied enormously from place to place not only in content but in enforcement. It would have been impossible to make any considerable journey with the assurance of being able to secure safe milk at all stops. Reported milk-borne outbreaks of infectious diseases were common while, doubtless, in the absence of any technique for their detection, many more failed to be noticed.

At that time the controversy over pasteurized versus raw milk was rising to its height. Very influential interests deprecated the heating of milk on the grounds that valuable nutritive principles were injured by heat. In a baby-feeding experiment conducted at the Hygienic Laboratory (1912–14) no difference could be detected between the progress of infants fed on raw milk of excellent sanitary quality and the same milk pasteurized. Due to unnecessarily high temperatures often employed in commercial pasteurizing, milk sometimes acquired a disagreeable taste, and the cream would not separate to a visible line in bottles, so that the housewife would have none of it. Studies made by Service workers and others showed that these difficulties could readily be overcome, and that whatever loss of vitamin the milk might suffer by heating could easily be compensated by the accessory feeding which every infant should have. The certified milk movement was correct in its insistance on healthy animals and attendants and on scrupulous cleanliness, and to that extent was supported by the Service; but it later became apparent that it was too costly for the ordinary consumer, and that even the elaborate precautions taken were powerless to prevent at all times the dangerous contamination of milk. This became apparent when actual outbreaks of disease occurred from the use of certified milk. The Service was obliged to throw its influence in the direction of encouraging universal pasteurization. However, pasteurization was still very imperfect. The process was used in some places to cloak the sale of dirty and diseased milk and to prolong its period of salability. Pasteurizing apparatus also was often defective and could not be relied upon to yield a safe product. The Service was equally opposed to these abuses and sources of danger.

The sought-for opportunity to study all these problems at first hand and in their complex relations to each other was afforded in 1923, when Frank, of the Service, was sent to Alabama in response to a request from the State health officer, Dr. Welch, for assistance in developing a State-wide milk program. The studies thus begun resulted in the formulation of a Public Health Service Standard Milk Ordinance, which has at this writing been adopted in 782 cities and towns in widely distributed parts of the country. Its success has apparently depended upon its reasonableness and fairness as regards the decent dairyman, and the almost automatic ease of its administration, while by markedly improving the sanitary quality of milk it has restored confidence in this product, and has led to a much-to-be desired increase of consumption (RPHR 1099, *1926*).

At almost every step in this public health program, bacteriology was called upon as a check and guide. The whole question of milk production, handling, pasteurization, and distribution had first and last to be bacteriologically reviewed.

Full-scale tests of pasteurizing apparatus were begun in 1926, many different models were investigated, their defects determined, and methods of correction devised (RPHR 1154, *1927*). The opposition of manufacturers, confidently predicted by some critics of this activity, proved to be temporary or inconsequential. In fact, these groups soon began to vie with each other in compliance with the suggestions for improvement offered by the Service, which was much to the public advantage.

A bacteriological investigation of the sterilizing of milk utensils and equipment, begun in 1931, has introduced an interesting feature which may have wider applications. The test organism, a strain of *B. coli communior* unusually resistant to heat, and for that reason selected as more than representing the most resistant of pathogens, is exposed in full size apparatus to the various temperatures and holding times. The feature in which these tests differ from many previous experiments consists in selecting as the end point not the killing of the last chance surviving organism but the point at which 99.99 percent of the organisms are killed. The mathematical advantage of this is evident when one considers the bizarre results of successive experiments which demand that the toughest bacillus which happens to be present in the mixture be killed.

Interesting results concerning the effect of cooling have also been obtained. For example,

> Milk at 50° F. shows less than twofold growth in 24 hours and less than tenfold in 48 hours.
>
> Milk at 60° F. shows enormous multiplication, up to 2,300-fold in 48 hours.

In 1932 another check-up on the relative growth-promoting qualities of raw and of pasteurized milk was made which involved 3,700 children from 10 months to 6 years of age. No difference could be found between the two groups (RPHR 1549, *1932*).

The following figures representing a 4-year advance in milk sanitation, not from the worst to the best, but just as a matter of gradual progress, were collected by the Service and may be of interest. The figures represent percentages of market milk produced as indicated, and distributed in cities of 10,000 or more population in the United States (AR *1932*, p. 49).

Year	Percent of milk pasteurized	Percent of cows tuberculin tested	Percent subjected to either measure	Percent subjected to both measures
1927	81.8	68.1	99.1	50.8
1931	87.5	88.0	99.83	74.5

As a result of a study of the sterilization of milk cans it was possible to state that hot air at 170° F. would devitalize all milk-borne pathogens (AR *1935*, p. 9).

The principles and the details of practice which are the result of the milk studies of the Service over a long period are brought together in the latest edition of the Public Health Service Milk Ordinance and Code (PHB 220, *1936*).

PELLAGRA

Pellagra is not a bacterial disease. The reasons for including a discussion of it in a history of bacteriology are that until its true etiology was cleared up by the Public Health Service its cause was speculative only, among the speculations being those of bacterial and bacterial toxin origin, and that a great deal of bacteriological study was expended in proving that it is not a bacterial disease. Thus, Tizzoni advanced his *Streptobacillus pellagrae* as the cause, while Ceni attributed the disease to an *aspergillus*. Lombroso believed it to be due to an intoxication from products developed in corn by bacteria during spoilage. A commission of able men in the United States concluded from epidemiological studies that it was an infectious disease because it was more prevalent in insanitary and unsewered portions of cities, missing the fact that the inhabitants of these areas were also poor and could not afford adequate diet. Sambon proposed a protozoan parasite transmitted by insects.

The Public Health Service had no dearth of theories to choose from when it became interested in this disease. In 1908 Passed Asst. Surg. Lavinder first brought to the attention of the Service the fact that cases of pellagra (nonreportable, of course) were being discovered in some Southern States—North Carolina, Georgia, and Alabama. He was directed to investigate further. He reported that it seemed to be much more prevalent than at first suspected, and estimated in 1909 that there had been some 1,200 cases since 1907. Aside from the significant public health problem opened up, there was the economic consideration that American corn was having difficulty in securing European markets because of the prevalent belief abroad that corn was responsible for producing the disease.

In 1910 Lavinder was sent to Europe to study the disease. His experience only confirmed his belief that the American disease was identical with the European, with the difference that our cases appeared to be somewhat more acute. In that year, at a national conference called by the State of North Carolina, the National Pellagra Conference was set up as a permanent body.

By 1911 the Service estimated that there had been 25,000 cases since 1907. It was apparently time to begin a serious study of this

relatively new menace. Proceeding on the infectious theory, Anderson, Lavinder, and Goldberger tried to infect monkeys with materials from pellagra patients, without success. A somewhat significant observation was made in 1912 by B. S. Warren of the Public Health Service. During an investigation of a Federal reform school where a case of pellagra had developed, he observed that sanitary conditions were excellent, but that the diet for inmates was deficient in meat and other proteins.

Surveys and other studies continued until 1914, when the investigations were systematized and greatly enlarged. Surg. Joseph Goldberger was placed in general charge of a research organization, which totalled some 41 persons. The studies planned included epidemiological, bacteriological, pathological, metabolic, and dietary researches.

The attempts to demonstrate a possible infectious agent were carried out with characteristic imagination and thoroughness by Dr. Francis. Over a hundred monkeys were inoculated by various means, as were numerous animals of other species. All attempts by Service workers (including the administration of the secretions and excretions of pellagrins to healthy human beings) to induce pellagra as an infection were unsuccessful (HLB 106, *1917*).

In the Public Health Reports for June 26, 1914 (Reprint 203), Goldberger announced his dietary deficiency theory. This was based on a very simple, but in retrospect very conclusive, fact which ran through all his own experience and that reported in all the literature available to him, namely, that in institutional pellagra it is always the inmates and never the attendants, doctors, or nurses who develop the disease. Infectious diseases do not behave in this way. Searching for influences which might affect the inmates and not the others, Goldberger could discover nothing apparently significant except the diet, which was, in fact if not on paper, markedly different. At this time he pushed the matter no further than to observe that the deficiency appeared to consist of such protein foods as eggs, milk, and meat.

In the following year (1915) the dietary hypothesis was put to test in a number of institutions where the Service had posted observers. The only changes made were in the substitution of a well-balanced diet for the one-sided, chiefly vegetable diet on which pellagra had appeared in a large proportion of inmates year after year. Of 172 pellagrins subjected to the new diet only one had a recurrence. In one institution where the new diet was given only to a portion of the inmates, 72 former pellagrins who received it escaped entirely, while of 32 remaining on the old diet, 47 percent suffered recurrence. (RPHR 307, *1915*).

During the same year Goldberger conducted the human experiment in convict volunteers, in 6 out of 11 of whom after some 5 months on a diet adequate in calories but deficient in protein constituents,

Dr. Joseph Goldberger, who as an officer of the Public Health Service demonstrated that pellagra is essentially due to a dietary deficiency. (Born July 16, 1874, died Jan. 17 1929.)

under otherwise ideal hygienic conditions, pellagra, confirmed by experienced dermatologists, began to develop (RPHR 511, *1915*) (HLB 120, *1920*).

The argument was now complete, and we shall pass over with bare mention the further developments—the narrowing down of the deficiency first to vitamin B, then to its thermostable constituent B_2 (also known as vitamin G); the induction by dietary means of blacktongue, the canine analogue of pellagra, the study of which has been most profitable to the canine species and the human race; and the practical determinations, continued to the present time, of the pellagra-preventing properties of numerous common foodstuffs, which have furnished valuable information to those whose income compels an inexpensive diet, and to health officials who must combat the disease.

It is known that there are some die-hards who still cling to the infectious theory of pellagra. Even if they grant some influence of diet, they propose an ultimate exciting cause among the micro-organisms. Some plausibility to these claims was offered in early days when individuals were found who, although affluent and able to command every table luxury, still had pellagra. Goldberger himself observed these cases until he found that, although the table might be laden with viands of all sorts, the patient, through some personal idiosyncrasy, selected only the wrong ones for his personal consumption. It is up to these objectors to produce the causative organism, and also to explain why, in prosperous years, pellagra almost disappears, to return again with hard times and limited diets, or that more recent refinement of epidemiology which shows that even in hard times, when the price of cotton is so low as to make it not worth while to plant, the cow and the kitchen garden which take its place entirely prevent pellagra.

We cannot, however, dismiss the subject without some reverent gesture to the man of all men who was chiefly responsible for the solution of this mystery of centuries, this health problem which was the despair of the authorities before his discoveries. Dr. Goldberger's other contributions to medical science would of themselves constitute an enviable record. His demonstration of the potential role of the head louse in endemic typhus, of the infectious period, incubation period, and susceptibility of monkeys in the case of measles, and even his minor contributions to the bacteriology of cholera and the anatomy of flukes, are all sound, useful, and original contributions. He illuminated everything he touched, and won the admiration and affection of his associates.

PLAGUE

The first severe test of the competency of Service bacteriologists may be said to have occurred in 1900, when suspected cases of bubonic plague began to come to the attention of the local sanitary author-

ities in San Francisco. Dr. Kinyoun, formerly the director of the Hygienic Laboratory, was then assigned to quarantine duty at that port. It was his duty to be informed of local health conditions, and he obtained materials from some of these cases and reported that he had confirmed them bacteriologically as plague. The same confirmation followed at the Hygienic Laboratory on specimens which he sent there. There followed one of the most sordid and distressing stories of sanitary annals, lasting over many months, extending to the city and State governments, into local politics, the press, the agencies of the law, and even threatening international complications. It is within the power of a few microscopic plants on a glass slide, granted certain antecedents, to cause such upheavals in the affairs of man. The health agencies appear from the record to have come through the melee with at least honor unimpaired, but the political agencies and the press made but a poor showing in the cause of public service. Even the law, which we must not criticize, gave an example of how decisions arrived at, presumably in accordance with its rules and traditions, may protect undeserving persons and do the public an enormous disservice.

To shorten a long and unsavory story and to get at the moral quickly, we shall simply give examples of what happened and not attempt a chronological account. The press presented a solid front not only in denying the existence of plague in San Francisco, but in belittling and hampering all those who entertained the opposite and true opinion. The city fathers seconded and inspired the press in its efforts. The commercial powers, including the great Chinese Six Companies, resorted to almost all conceivable tricks of intrigue and even violence to suppress knowledge of the true state of things. Kinyoun was alternately threatened and offered large bribes to recede from his position. Plots were made to destroy the patrol boats under his jurisdiction which attempted to prevent the smuggling of Chinese, well, sick, and dead, out of the city. The Navy had to be called in to give them protection. An injunction against sanitary interference in Chinatown was granted by a circuit judge. Kinyoun was cited in contempt of court on trumped-up charges. The Governor of the State accused the health authorities, local and Federal, of incompetence and the use of illegal and unfair methods, and denied absolutely the existence of plague. And all this and much more because of the fear that if plague were publicly acknowledged, business prosperity would suffer. And what were the actual conditions? Some 25,000 Chinese lived in the section known as Chinatown. A few of them were wealthy and lived in sumptuous surroundings, but the majority lived under conditions which should never have been permitted on American soil, conditions of overcrowding, squalor, and degradation almost incred-

ible to the eyes of the sanitary squads, when, after many months, they were finally permitted to go in and clean up. In this population plague had doubtless been smouldering for weeks before the first case came to light; but with all the oriental arts of craft and ingenuity, the prying eyes of the health authorities were kept from seeing what was going on. Sick and dead Chinese were smuggled out of the city or otherwise disposed of so as to keep them from inspection. Persons sick for a day or two with buboes were represented as having been sick for a month with some chronic disease. This was the population which the press and the politicians, the law and business, arose in sanctimonious wrath to protect in its inalienable civil and legal rights. It was estimated that during the period of the injunction some 1,000 Chinese left the city in 1 week, seeking refuge, in the surrounding cities, villages, and countryside, from the pestilence which they recognized only too well. Does the chronic infection with plague among ground squirrels involving a large area in California, a constant menace and already the cause of many human deaths, date from this exodus?

As a final measure to meet this apparently hopeless situation, the Secretary of the Treasury, at the suggestion of the Surgeon General, appointed a commission of impartial experts, Flexner, Novy, and Barker, to make an independent investigation. Although snubbed by the university where they sought laboratory space, and browbeaten by the Governor, they persisted and in a short time brought in a verdict of plague (PHB 8, *1901*). Of 13 deaths investigated, 6 were found bacteriologically to have been due to bubonic plague. After this, opposition smouldered and finally died out. The Public Health Service was asked to clean up Chinatown, and actually performed this Herculean feat, and for the time San Francisco was free from plague.

Of course plague came back to San Francisco. The history of many a progressive and prosperous city, such, for example, as Liverpool, has shown that the infection, once established in the rat population, is difficult to eradicate. During the years first of desolation and then of recuperation, cleaning up, and rebuilding which followed the San Francisco earthquake and fire of 1906, plague quite naturally reappeared with redoubled vigor. The wreckage of the buildings and sewers, the accumulation of vast amounts of rubbish, the flimsy construction of temporary abodes, the disorganization of food handling and garbage disposal, afforded ideal conditions for rat multiplication. It is instructive to reflect that under such conditions, and in the presence of an abundance of fleas, one old rat with chronic plague could start an epidemic.

At the time of the earlier epidemic, the Hygienic Laboratory was turning out large quantities of Haffkine prophylactic for use in the

plague-threatened areas, this rather than the control of the rat population being considered at that time the chief reliance (AR *1900*, p. 676), and experiments were conducted to determine the viability of the bacillus on various objects (ibid. p. 603).

During this epidemic a plague laboratory was set up by the Service in San Francisco, which, with the exception of about 3 years of quiescence, has been maintained in various quarters up to the present time. Here Currie in 1903 described chronic plague in the rat, since recognized as an important factor in maintaining infection. In the following years, under the direction of McCoy, a great many studies pertaining to the disease were made, dealing with such subjects as the infectibility or resistance of various species of small animals, the pathology of rodents with plague, bacteriological methods, the role of various fleas, and the bionomics of rodents. In the latter connection it was found that when *Rattus norvegicus* had been significantly reduced in numbers by the campaign, the other varieties, *R. rattus* and *R. alexandrinus*, rapidly increased, introducing new factors into the control program because of their different habits (AR *1912*, p. 152). It seems unnecessary to refer to these contributions categorically. They were very useful to Service officers in following plague campaigns (New Orleans, Hawaii) and played their part in building up the present-day conception of the disease and its bacteriology. During the New Orleans campaign C. L. Williams showed that routine microscopic examination of rat spleens and livers reveals infection in some cases (35 percent of total plague rats) not discoverable macroscopically (RPHR 357, *1916*). It is, perhaps, worth recording that in this outbreak plague rats were not discovered until several thousand of them had been examined, showing how focal the infection may be in such cases. The remarkable retention of viability and virulence of nontransferred agar cultures of the plague organism (9 years) and of the organism in guinea pig spleens in glycerin at −15° F. (7 years) is reported by Francis (RPHR 1535, *1931*).

The antiplague activities of the Public Health Service, in the absence of any recent human outbreaks, have now sifted down to three: Trying to keep shipping free from rats (C. L. Williams, RPHR 1267, *1929*) (Grubbs and Holsendorf, SPHR 93, *1931*), perennial supervision of the so-called plague-free zones around California cities, and the control of rural plague in Hawaii, where the disease is epizootic in field rats and a new species of fleas, *Xenopsylla hawaiiensis*, appears to be the common transmitter (AR *1933*, p. 9) (Eskey, PHB 213, *1934*).

While other Pacific coast cities besides San Francisco have been visited by plague, and there have even been small outbreaks of the

pneumonic type, the human mortality has fortunately been small although rat infection has sometimes been considerable. The history of plague in Seattle has recently been written interestingly and completely by Fricks (PHB 232, *1936*).

Plague has possibly come to be regarded by Americans as an exotic disease of historic interest only, or at least confined to relatively undeveloped countries and populations. Probably few realize that the disease is firmly entrenched on our own territory, among the ground squirrel population of the far West, and that only by eternal vigilance has it been prevented from invading the rat populations of cities, and from them infecting human beings. While eradication may appear well-nigh impossible, more favorable conditions of attack have been afforded by some of the health provisions of the recent Social Security legislation. Mobile laboratories have been successfully used in locating foci of infection.

POLIOMYELITIS

Poliomyelitis, by its increase in the United States at a constantly advancing rate, had, by about 1910, become of sufficient public health importance to excite Nation-wide concern. In this year Frost, of the Public Health Service, voiced this concern, reviewed existing knowledge regarding the disease, and outlined the directions which its study should take (RPHR 55, *1910*). Opportunities soon presented themselves for the field study of the disease, and the question of the method of transfer became of paramount interest. Richardson, of the Massachusetts State Board of Health, was led by epidemiological considerations to suspect the agency of the stable fly, and Rosenau, then of Harvard, demonstrated the possibility of transfer from monkey to monkey through the bite of this fly. Anderson and Frost were at first able to substantiate this work experimentally (RPHR 99, *1912*), but subsequent repetitions of the experiment at another season of the year resulted negatively (PHR *1913*, p. 833). The authors were unable to explain this discrepancy except, perhaps, on the basis of some unknown effect of season. Further epidemiological studies by officers of the Service soon convinced them that *Stomoxys calcitrans* could play no determining part in the transfer of the disease, although occasional transmission by this means remained a possibility. During the winter outbreak of poliomyelitis at Elkins, W. Va., in 1917, studied by Leake, Bolton, and Smith, no history or evidence of the presence of this fly could be elicited after diligent search (RPHR 437, *1917*).

The phenomenon of the neutralization of the virus of poliomyelitis *in vitro* by the serum of recovered monkeys and persons had been demonstrated by Flexner and Lewis, and by Netter, and the latter

had apparently shown in one instance that it could apply also to the abortive case. Anderson and Frost investigated nine cases of so-called abortive poliomyelitis (cases in which the symptoms fell short of paralysis) and demonstrated the phenomenon in six of the patients, who, as it happened, were adults. In the three remaining, who were children, the test was negative. These authors showed a creditable restraint in their interpretation of these results. Indeed, in the light of present knowledge, interpretation of the whole phenomenon must remain somewhat speculative. Possibly the most significant outcome of the study was the fact that supposedly normal human serum could exhibit the neutralizing property, although in a relatively feeble degree (J. A. M. A., *1911*, **56**: 663). In view of the present conception that in this disease subclinical infections far outnumber the recognizable cases, is it not a plausible assumption that the six adults of this series were abortive cases because of a pre-existing relative immunity, evidenced by neutralizing properties of the serum enhanced by the recent attack?

The Service has been engaged in a number of intensive epidemiological studies, which, although excellent in their way, have done no more as regards bacteriology than to confirm to a large extent the conceptions of cause and methods of transfer resulting from laboratory work. The most extensive of these was in connection with the great outbreak of 1916 in New York and the northeastern States, reported by Lavinder, Freeman, and Frost (PHB 91, *1918*). Further laboratory work by various Service personnel (HLB 111, *1918*), while confirmatory of much current belief, failed to substantiate the infectibility of small laboratory animals (aside from monkeys), and the cultivation of the virus on artificial media which was claimed by some observers.

The most recent contributions of the Service to this problem are those of Armstrong and Harrison. As it had been shown by the former that previous treatment of the skin or mucous surfaces of experimental animals with certain irritant substances (diphtheria toxin, alum solutions) could have a restraining or modifying action upon subsequent inoculations with the viruses of encephalitis and vaccinia (PHR *1933*, p. 1) (PHR *1935*, p. 43), the principle was applied experimentally in the case of poliomyelitis virus. Nasal instillations of alum solutions in monkeys were found to be highly potent in preventing the success of subsequent intranasal inoculations of monkeys with poliomyelitis virus (17 survivals out of 23 treated with alum, against 3 survivals out of 10 untreated controls) (PHR *1935*, p. 725). Various agents were then tested in mice against the encephalitis virus (to avoid the expense of numerous monkey experiments), and the most promising were then employed in monkeys. Picric acid alone or in combination

with alum made the best showing of all the agents employed in the mouse tests, and it was then employed in the monkey tests with poliomyelitis virus. This agent (alone or in combination with alum) again demonstrated great efficacy in preventing infection by subsequent intranasal inoculations (PHR *1936*, p. 203). About 90 percent of the treated animals survived, while 90 percent of the controls died. Similar experiments were then tried, using the intravenous method of inoculation, on the theory that infection of the nervous system following this method is only by means of blood stream infection of the nasal mucosa. Again marked protection was afforded though in less degree than with the intranasal inoculations (PHR *1936*, p. 241). The marked and unidirectional results of all these experiments would certainly seem to justify the hope of the successful application to man of the principle for the prevention of the spread of the disease during epidemics. A suitable technique for application to children, and the choice of the best preparation to use, remain to be determined.

PSITTACOSIS

In 1929 an unusual form of illness somewhat resembling both influenza and typhoid fever began to be reported from various parts of the United States. Some foreign countries had the same experience. Association of the patients with sick parrots was soon noted, and the disease was identified as psittacosis. In the United States 169 cases were reported from November 1929 to May 1930, with the high death toll of 33 cases. The Public Health Service took prompt action under an executive order restricting the importation of parrots, but the aviaries of some local bird dealers became infected, and it was necessary to impose interstate restrictions and a system of quarantine against the birds before the disease died out, and even then there were isolated recurrences for several years.

Studies of the disease were immediately begun at the National Institute of Health. At that time the disease was universally believed to be due to Nocard's *B. psittacosis*, and the studies were begun with that assumption. All attempts to isolate this organism, however, proved futile (Branham, McCoy, and Armstrong, RPHR 1411, *1930*). On the other hand, early filtration experiments were successful (RPHR 1363, *1930*), and the disease soon became recognized as due to a filterable virus. During the course of the experiments, which had been undertaken with what appeared to be ample precautions, an outbreak occurred among the personnel at the National Institute of Health, involving 11 persons, 1 of whom died. This would seem to indicate an almost incredible diffusibility of the infection through the air, since some of the victims had not been nearer to the rooms in which the animals were kept behind moist curtains, and with troughs of disinfectant

at the doorways, than to pass to and occupy rooms in distant parts of the large buildings. This has led to the assumption that the virus may be spread by the "powder down" thrown off by parrots, which seems to have a diffusibility comparable to the pollens. Contributions to the epidemiology of psittacosis were made by Armstrong (RPHR 1406, *1930*) and by Badger (RPHR 1386, *1930*), who studied an interesting outbreak in a department store where a parrot exhibit had been featured. The pathology of psittacosis in man and animals was studied by Lillie (NIHB 161, *1933*).

During this outbreak officers of the Service had the opportunity to contribute, to use, and to observe the effects of convalescent serum. Although its administration sometimes appeared dramatically beneficial, as observed by lay patients and some clinicians, the scientific personnel of the laboratory appears to maintain a very conservative attitude towards its efficacy.

RABIES

During the early years of the Hygienic Laboratory some of the officers connected with it had had the opportunity to study rabies and the Pasteur treatment in Europe, and some experimentation was done after their return. By 1906 the question of the prevalence of this disease in animals and the exposure of persons to the bites of dogs had become so acute that action on the part of the Public Health Service became necessary. At that time there were several so-called Pasteur institutes in the United States, managed for the most part by men who had studied at the Paris institute, at which preventive inoculations could be obtained. These were few in number and widely separated; and since the vaccine was not then sent out by manufacturing firms, it often happened that exposed persons would have to travel many hundreds of miles to secure treatment, which not only occasioned delay and great expense, but effectually prevented many persons who required it from getting the treatment. The study of the disease was, therefore, resumed at the laboratory, the literature was reviewed, and a method of treatment based on Pasteur's original method was adopted. This was administered to patients who applied at the laboratory beginning April 29, 1908. A method of preserving glycerinated spinal cords of rabbits and shipping portions adapted to the preparation of emulsions to State health officials having laboratory facilities was devised and carried into effect. After this, exposed persons in any part of the country had to travel no farther than to their own State health office for treatment. This practice was continued until 1921, when the development of a satisfactory service by several manufacturers of biological products made its further continuation unnecessary.

A survey of the prevalence of rabies in man and animals in the United States was conducted by the Service for the years 1908 (Kerr and Stimson, PHB 29, *1909*) and 1911 (Stimson, RPHR 87, *1912*). An unexpected finding of these surveys was the fact that human cases reported in the newspapers and traced from a clipping service could be medically verified in nearly all instances. The human deaths appeared to vary around 100 per annum, while the cases in dogs and livestock ran up into the thousands.

The review of the subject and special studies at the laboratory were reported in HLB 65, *1910*. During the administration of the treatment at the laboratory, the phenomenon, presumably an allergic one, of the flaring up of the injection sites with an edematous erythema was observed and apparently described for the first time (Stimson, J. Med. Res., *1910*, **23**: 511). Several instances of paralysis attributed to the Pasteur treatment were observed during this experience, and the condition has been discussed in several papers.

RATS

Rats have played such a large part in the studies and control activities of the Public Health Service that they would seem to deserve some special mention. Omnipresent as they are, and tending always to breed to the limits of the environment, even in the face of persecution, it is fortunate indeed that they are not the vectors of more human diseases than have so far been attributed to them.

The knowledge of the time regarding the sanitary and economic significance of rats was brought together in PHB 30, *1910*. In the studies of plague, tularaemia, epidemic typhus, rat leprosy, and other diseases, rats have played significant roles in the research work of the Service, and still more so in the practical matter of rat eradication. All conceivable methods of combating this nuisance and menace appear to have been tried out on a practical scale, including the use of viruses intended to induce epizootics among rat populations, poisons, both mineral and vegetable, traps of various kinds, lethal gases, the destruction of breeding and sheltering places, and finally building them out on shore by concrete and wire mesh, and on shipboard by modifying the construction details of vessels. All of these measures are dealt with in Service publications. Dr. Harry White, of the Service, has prepared an extensive cinema film depicting the life history, depredations, and methods of combating the inroads of rats.

The danger of transporting plague by ship rats is, of course, a very real one, which is being met by the Public Health Service not only in preventing the landing of rats from vessels, but by a systematic endeavor to render ships which touch at American ports as free from rats as possible, and to encourage forms of construction

inimical to rat harborage. The number of rats a ship may carry is almost incredible except to those who have seen it at first hand. The story is told by one of our officers that while engaged in ship fumigation on quarantine duty he was approached by an acquaintance who desired some dead rats for a scientific study he was making. In reply to the question as to how many he wanted he said, "Oh! not so many. Say what you get off the next ship." Eleven bushels of dead rats were duly delivered on these specifications. This is not cited as an extreme case but just as a part of an ordinary day's work at that time and place.

Specific references are given under the various diseases in which rats play a role. The compensatory function which the rat tribe furnishes as an experimental animal in many lines of laboratory work, including nutrition studies, should, perhaps, be entered on the credit side of the account.

RELAPSING FEVER

Relapsing fever is fortunately localized in certain areas in the West and Southwest, especially in Texas and California, as far as American experience goes. It differs from Old World forms in having no mortality (in some 350 cases) and in being transmitted, so far as is known, only by the ticks *Ornithodoros turicata* and *O. hermsi*. Certain caves in Texas are infested with infected ticks, and visiting persons or animals run a chance of becoming infected.

The Public Health Service is interested in this infection and has made a number of confirmations of diagnosis in human cases and a few original observations concerning it. Francis has shown that naturally infected ticks can transmit the infection through their eggs to their progeny, and that artificially infected bedbugs can harbor the infection for at least 6 months, as shown by injection of their ground-up bodies into mice, although their bites are innocuous (Trans. Assoc. Amer. Physicians, *1932*, **47**: 143). His latest experiments show that naturally infected adult ticks, *O. turicata*, collected in Texas and kept without food for 5 years, still infect monkeys when allowed to feed on them (AR *1936*). The bearing of these facts on the control of the disease is apparent.

ROCKY MOUNTAIN SPOTTED FEVER

The spotted fever of the Rocky Mountains is said to have been observed in white settlers in Montana and perhaps in bordering States as early as 1872, and some evidence of its prevalence in Indians has been obtained. Its peculiar and deadly attacks in the Bitterroot Valley of Montana led to much anxiety on the part of the State health officials, which culminated in 1902 in their invitation

to Drs. Wilson and Chowning of the University of Minnesota to make a local study. A peculiar feature of the disease was that it attacked residents on one side of the river running through the valley but not those on the other side of the stream. It had a well-marked seasonal prevalence during the spring and early summer, and a clinical resemblance to typhus fever.

In the same year (1902) in which Wilson and Chowning began their studies, the Public Health Service sent an officer, Dr. Cobb, to investigate the situation. He reported on the outstanding features of prevalence and extent, clinical course, and prevailing theories as they were understood at that time. Since then the Service has had one or more officers on the ground during at least a part of nearly every year. Since 1922 it has maintained a field laboratory at Hamilton, Montana, for the study of the disease, and for the preparation of a vaccine for its prevention since 1925. Anderson, who made studies during 1903, was inclined to accept the tick hypothesis of transmission and the *Piroplasma* etiology advanced by Wilson and Chowning. He listed reported cases from 1885 on and contributed a valuable summary of what was known concerning the disease (HLB 14, *1903*). Stiles, who visited the region in 1904 and approached the subject largely from the zoological viewpoint, was unable to support the finding of *Piroplasma* in the blood of patients, the infectibility of rabbits, or the tick transmission ideas of his predecessors (HLB 20, *1904*). Francis was on the ground in 1905 but apparently regarded definite pronouncements as premature since no publication followed his investigations.

In 1906, W. W. King produced the disease in guinea pigs and monkeys by injections of blood from patients and in a guinea pig by feeding an infected tick upon it (PHR *1906*, p. 873). The results were practically simultaneous with those of Ricketts, who was pursuing his memorable studies at the same time.

In 1909 Goldberger and Anderson, in Mexico City, studying typhus fever, thought that their apparent failure to produce that disease in guinea pigs might be a useful point of differentiation from spotted fever, but their investigations were interrupted by Goldberger's attack of typhus, and it was only upon a review of their protocols a year later that they concluded that the temperature charts of the animals really indicated successful infection (HLB 86, *1912*, p. 103).

In 1911 and 1912 McClintick pursued studies at Victor, Mont., which were terminated by his death from a laboratory infection with the disease in 1912, this being only one of a series of such fatalities which have occurred during the Service work on this disease. Both McClintick and Fricks, who followed him, gave much attention to the problem of animal hosts which perpetuate the disease in nature and found them chiefly among the small rodents, since the larger quadrupeds were apparently immune. Cattle and sheep, however,

were recognized as important carriers of ticks from place to place, and the practice of dipping cattle was advised by McClintick for this reason, while Fricks thought that sheep might actually be used to collect ticks in infected territory and remove them to uninfectible regions. In laboratory studies Fricks (RPHR 327, *1916*) showed that the virus could be separated by centrifugation from blood serum, and he described stained forms in red blood cells of infected animals which he did not find in controls.

These early investigations have been referred to in some detail partly because they illustrate the difficulties encountered in studying a new disease, how interpretations may differ unless the key is known, and how simple explanations at first advanced by parallel reasoning may not suffice; and partly for the opportunity of saying that during these years a large volume of valuable information was gained which found its place in the later developments, such as the reality of tick transference, the exact distribution of human cases, the seasonal prevalence, the variation of virulence, the life histories of ticks and their rodent hosts, the contrasts between blood virus and tick virus, the clinical course and diagnosis of the human and animal disease. These contributions were to be developed, refined, and employed in the more accurate and profitable work that followed.

When the Service assumed charge of the Hamilton laboratory in 1922, more favorable conditions for continuous research were provided. Spencer and Parker were associated for a period of some 10 years in a series of profitable studies which have been collected in large part in HLB 154, *1930*. The outstanding feature of this work is the preparation and distribution of a vaccine intended for the prevention of the human disease. While the principle involved had been demonstrated on a laboratory scale by Breinl in the case of typhus fever and by Ricketts as regards spotted fever, its application to human beings and on a large scale must be regarded as a bold and original step. Since the virus was not cultivable artificially, recourse was had to the infected tick itself as a source of the vaccinial material.

The task of tick eradication in a heavily infested area, such as the Bitterroot Valley, has resisted all efforts made by such mechanical, chemical, and biological methods as have been suggested and tried. When we consider the natural qualifications of these animals for survival, such a task may now be accepted as impossible by any means at present known. The eradication of small rodents which act as hosts for the ticks and probably for the disease is also an undertaking of great difficulty, involving great expense and having slight per-

manency. The alternative is, therefore, the immunization of the exposed population, and this is what the vaccination procedure attempts to accomplish.

Preliminary studies had shown a number of facts which it was essential to appreciate before the preparation of a vaccine from ticks could be undertaken. One of these was the remarkable augmentation of virulence which results from the blood feeding of an infected tick. Before such a feeding the bite of a tick may result in no observable symptoms in a guinea pig, although the animal may be proved by subsequent tests to have acquired immunity. After a blood meal, however, the 5,000th part of a tick may be fatal to guinea pigs when injected into them. It was found that a phenolized emulsion of ticks which had had a blood meal would protect guinea pigs (later

Rocky Mountain Laboratory at Hamilton, Mont.

also rabbits and monkeys) against otherwise fatal amounts of virus; and shortly afterwards Spencer took injections of this material to demonstrate its harmlessness in the human subject. The next step was to inject all the personnel of the laboratory engaged in tick work. The results being apparently favorable, the manufacture of this vaccine and its administration to sheep herders and others whose work involved much exposure to tick bites was begun on an increasing scale (HLB 154, *1930*). The demand for this vaccine has at times exceeded the capacity of the laboratory to prepare it, although large amounts have been furnished. Until 1930 the method of preparation was extremely tedious and time-consuming, involving as it did the raising of ticks from eggs, infecting them as larvae, allowing them to go through two moults, blood-feeding the adults, and preparing the emulsions, together with all the incidental control tests on virulence

and on the sterility of the product. In that year an account of a somewhat simplified method was published (idem).

The usefulness of this product can hardly be questioned, although it has been impossible to collect statistics which have the value of a well-controlled experiment. As in all similar operations the difficulty lies in obtaining a thoroughly representative control population. The vaccine does not protect against infection with the more virulent strains in 100 percent of those receiving it, although it apparently markedly reduces the incidence. It does seem, however, to have a life-saving potency of great value. Such cases as have occurred after the use of the vaccine have for the most part been surprisingly mild, according to the observation of physicians accustomed to the virulent infections occurring in the same vicinity in nonvaccinated persons. In areas where the infection is of low virulence, complete protection is usually afforded.

The later developments of interest concerning spotted fever concern principally the discovery of an apparently almost identical disease, not only outside the Rocky Mountain area, but even in States along the Atlantic seaboard. This form produces cross immunity with the Rocky Mountain form, but not with typhus fever, as shown by Badger, Dyer, and Rumreich (PHR *1931*, p. 463). The same authors showed that it is commonly transmitted by the dog tick, *Dermacentor variabilis*, which is locally prevalent in the East, as the wood tick, *Dermacentor andersoni*, is in the Rocky Mountain area (RPHR 1483, *1931*). This eastern form appears at present to be distributed in rather sharply marked foci, where it is acquired by picnickers or others who go into the woods during the tick season, spring and early summer, or who may be infected while removing ticks from dogs.

Spotted fever has been shown to give the Weil-Felix agglutination reaction with *Proteus* organisms in a considerable proportion of cases late in the disease or during convalescence, contrary to the belief of some earlier investigators (Spencer and Maxcy, RPHR 1357, *1930*).

A great number of contributions have been made by Service officers, many of them original, to which separate references can hardly be made here. They affect such questions as the nonfilterability of the virus, its tendency to remain with the white and red blood corpuscles on centrifugation but not with the platelets, the susceptibility versus the immunity (natural or acquired) of many species of animals, the lack of correlation between Rickettsiae prevalence and virulence in ticks, the exaltation of virulence by blood feeding and by incubation, and the aestivation and hiberation of the virus.

The gross and microscopic pathology of the eastern type has been studied by Lillie in material from five human autopsies, and certain

differencies from the descriptions of the western type have been brought out (RPHR 1516, *1931*).

The close relationship between Rocky Mountain spotted fever and the exanthematic typhus of Sao Paulo, Brazil, has been shown by immunological tests by Parker and Davis (RPHR 1568, *1935*) and Dyer (RPHR 1571, *1933*), and the same relationship to the boutonneuse fever of the Mediterranean littoral by Badger (RPHR 1570, *1933*). As far as these tests are able to disclose, these diseases are identical.

The most recent development of importance is the cultivation by Bengtson of the virus of spotted fever in chick embryos. The virus was carried through 20 passages without diminution of virulence; indeed the incubation period became somewhat reduced (RPHR 1711, *1935*). Rickettsiae were found in these embryos so far removed by passage from the original material that their close relationship to the virus is strongly suggested, in spite of the observations recorded above, that their prevalence is not an index of the virulence of tick virus.

SEWAGE DISPOSAL

The easiest way to dispose of sewage and other waste is to throw it into the nearest water course and forget about it. This is the system of choice employed in the early history of all cities in all lands, including the United States. The hitch comes when a community down the river objects to these tokens of upstream habitation and prosperity, and threatens or commences a law suit. When long distances separate the cities, natural purification may be sufficient to avoid controversy for a time; but as the population grows and as industrial wastes increase, the question of responsibility for the pollution of streams comes sooner or later. Since many of our streams run from one State to another, the question becomes one which can be interpreted as a Federal one. Nevertheless, either on account of altruistic principles or a wholesome regard for the results of legal proceedings, it is a fact that recourse to the law has been taken in only a few, though notable, instances. In some of these the Public Health Service has been consulted as a fact-finding agency.

Two other activities of the Service have been intimately bound up with its studies of sewage disposal—the studies of stream pollution and purification which are discussed in the chapter dealing with "Water" (see p. 72) and the studies of typhoid fever (p. 64). Under the former, attempts were made, with considerable success, to define the degree of permissible pollution of streams with due regard for the natural conditions of dilution, stream flow, and distance. Under the latter the unbearable condition of typhoid prevalence was forcibly brought to public attention, and the need

for limiting pollution, on the one hand, and increasing purification on the other hand, was emphasized.

The Public Health Service has not felt that it was its business to enter the field of plant design in competition with practicing engineers, who in general have exhibited a high degree of competence. Where failures have occured, they have been due rather to faulty operation than to imperfections of design, as shown by the surveys of Wagenhals, Hommon, and Theriault (RPHR 761, *1922*) (PHB 132, *1932*). The Service has, therefore, confined its researches rather to the elaboration of general principles and the perfection of tests, both of which could prove useful in future design and operation. To this end two experimental plants were constructed, each receiving its sewage from a small community. One of these was so constructed by means of connections that various sequences of processes could be studied, the other was designed to test out problems of performance and maintenance in a suburban community over a period of years. From these studies the Service obtained first-hand data on many of the bacteriological and chemical factors involved (Phelps RPHR 504, *1919*) (Frank and Rhynus PHB 101, *1920*). A little later the methods in use throughout the United States were studied by Hommon and others, who visited plants in various parts of the country and reported on the relative advantages of various designs and methods (RPHR 580, *1922*) (PHB 132, *1923*).

Following these preliminary studies the Service contributions to this subject became merged into its general researches of stream pollution (see chapter on "Water"), and have only recently been resumed as separate undertakings. During the last 2 years attention has been directed to the phenomena attending the clarification of sewage by activated sludge. Dissolved oxygen studies are essential to the measurement of these changes, and a special apparatus has been devised by Theriault for its determination in sludge-sewage mixtures (RPHR 1680, *1935*). Butterfield has succeeded in isolating in pure culture from activated sludge, by special bacteriological technique, a *Zooglea* organism of unusual interest. This organism produces a floc in both synthetic media and in sterilized sewage, and has the remarkable property of removing from 41 to 84 percent of the oxidizable material in polluted water in the short space of 3 hours. He considers it to be probably a variety of *Zooglea ramigera* (RPHR 1686, *1935*). Theriault, in RPHR 1715, *1936*, discusses at length the current theories regarding the mechanism of the clarification of sewage. He gives reasons for the belief that clarification is due to an absorbent principle having base-exchanging properties similar to those of the zeolite concerned in water purification. It remains to be seen whether a relationship between the *Zooglea* of Butterfield and this principle of Theriault can be established.

SHELLFISH

During the Potomac River survey of 1914, some 5,000 oysters were examined bacteriologically by Public Health Service investigators at the same time that the conditions of purity or pollution of the waters from which they were taken was determined. In this way the Service secured first-hand information on the potential health menace offered by food shellfish. In the following year extensive field surveys were made of oyster-bearing waters, and a laboratory for field studies was set up on Fisherman's Island in Chesapeake Bay. In the meantime some outbreaks of typhoid fever had been attributed to oysters, and the Service had found insanitary conditions in the associated shucking houses (AR *1916*, p. 40). The surveys by the Service of oyster beds were extended until they finally included practically all of the important areas in the country. It was not until 1925, however, that the State agencies concerned were sufficiently aroused to demand some organized and concerted action looking to the sanitation of the shellfish industry. This was brought about largely by the almost simultaneous outbreak of typhoid attributed to shellfish in Chicago, New York, Washington, and elsewhere. Dr. Lumsden, who was assigned to the study of these outbreaks, confirmed their origin in contaminated oysters. A conference of State health agencies with the Surgeon General passed resolutions leading to the adoption of uniform methods of control under the general supervision of the Public Health Service, and an appropriation was obtained from Congress for carrying out Federal investigations and control. Since that time the Service, in cooperation with the Bureau of Fisheries and the Bureau of Chemistry, and also with the State health officers, has been engaged in applying continuously more effective measures for the sanitary control of the culture, handling, and shipping of shellfish.

Of course, bacteriological examinations have accompanied these activities at each step, and many efforts have been made to improve technique. However, there are some inherent difficulties in the bacteriology of this problem, associated with the habits and physiology of the shellfish themselves, which interfere with the desired precision of determinations. Bacteriology, for the present, must therefore remain the assistant and advisor of the sanitary survey rather than its dictator. Tarbett has shown (unpublished data) how the distribution of contamination throughout the liquor and the various anatomical portions of the oyster must affect bacterial determinations intended to establish a score.

The hope was entertained at one time that shellfish taken from beds which might be under some suspicion from a sanitary standpoint could be purified and made fit for consumption by chlorina-

tion, much as milk, which is at all times under some suspicion, may be rendered sanitary by pasteurization. The studies of Wells (RPHR 351, *1916*) and of Carmelia (RPHR 652, *1921*) indicated some of the possibilities and limitations in this direction. However, as a practical procedure for the purpose indicated, chlorination is not employed in American practice, one reason being that the shellfish, contrary to expectation, do not drink the chlorinated water, but close up tight until its concentration becomes very much reduced. Chlorination is used in connection with shellfish culture, but merely to provide a sterile water on which the bivalves may be conditioned after the dissipation of the chlorine. Conditioning is the term employed by Tarbett to designate the process by which the shell liquor habitually ejected by the animal when brought to the surface and relieved of the pressure to which it has been accustomed, is replaced by a new supply administered in shallow beds, as a necessary preliminary to marketing and shipment.

TRACHOMA

Trachoma was for many years the bugbear of officers of the Public Health Service who were detailed to the medical examination of immigrants. Especially during the period of heavy immigration from the Mediterranean area and Russia, these officers were much occupied with this disease. There was no criterion for diagnosis beyond the clinical appearance and the therapeutic test. Doubtful cases, often in large numbers, were remanded to immigration hospitals for observation and treatment with astringents. If the condition cleared up during this period, it was considered granular conjunctivitis; if not, it was diagnosed as trachoma. This painstaking and costly procedure was necessary because trachoma was a condition requiring exclusion or deportation of the immigrant. The disease was very prevalent among immigrants from the areas mentioned. Since the costs were largely borne by the shipping companies, some of the latter instituted medical examinations of their own which weeded out a considerable proportion of the cases before embarkation. Later the Public Health Service stationed officers at the chief foreign ports to detect these cases before they received consular visas. Finally immigration was greatly restricted by law, and the problem became much simplified.

In the meantime attention was drawn to the prevalence of trachoma in our native population, and the Service conducted numerous and extensive surveys, especially among the Indians and the mountaineer groups, to determine its exact extent. This was found in some cases to be very high, and to require special measures for its control. Hospitals were established in several of the Eastern mountain States

where the afflicted could be received for treatment, and many hundreds were saved in this way from invalidism or blindness. These hospitals were conducted for the most part by Service medical officers.

The foregoing is only a prelude to the statement that bacteriology has not thus far been of any considerable assistance in this activity. Confronted by the same problems, the Service would have to proceed in the same manner as in the past. This is not for lack of serious attempts to solve the etiology of the disease. In 1924 Dr. Ida Bengtson, whose competence as a bacteriologist has been demonstrated in many fields, was placed in charge of a research laboratory at Rolla, Mo., which was well equipped and furnished with a wealth of clinical material. Her 8 years there were occupied with incessant work on the trachoma problem, utilizing all known techniques and reviewing the work of all competent claimants, but still the essential etiology of the disease remains unsolved (RPHR 1242, *1928*) (RPHR 1548, *1932*).

TUBERCULOSIS

The investigations of the Public Health Service with regard to tuberculosis have been for the most part clinical, epidemiological, and therapeutic rather than strictly bacteriological. Since the organism was already known at the time the Service entered the laboratory field, and a great flood of improved bacteriological procedures was being contributed year by year, there was little need for pioneer work on the part of the Service in this branch of bacteriology.

The treatment of tuberculous patients at marine hospitals having proved unsatisfactory, as was repeatedly pointed out by officers of the Service, a sanatorium was opened at Fort Stanton, N. Mex., in 1901, which has had a very active and successful career and has given opportunity for a great variety of clinical studies. Bacteriology has, of course, played a large part in them but it consisted mostly of the employment of recognized procedures.

The epidemiological studies have been concerned chiefly with two main topics—the problems arising from the migrations of the tuberculous in search of benefit by climate, and the relations between tuberculosis and industry, principally in the dusty trades, in which connections many and valuable studies have been performed. These again have employed rather than contributed to bacteriology.

The therapeutic studies have concerned chiefly investigations of various "cures" for tuberculosis, of a bacteriological or serological nature, which were conducted under the Biologics Act and are discussed under another heading.

For a number of years the Service has been associated with an organized research program fostered by the National Tuberculosis

Association, in which the scientific problems are being approached from several coordinated angles. There are, however, no Service publications on the bacteriological factors involved.

In the early days there was much discussion in Public Health Reports concerning "Koch's lymph", and a good deal of laboratory work was done in connection with it.

A study of complement fixation in tuberculosis was reported in 1914, and some value, especially of a prognostic nature, was indicated (Stimson, PHB 101, *1914*). The subject has recently been revived in scientific circles.

TULARAEMIA

The elucidation of the essential features of tularaemia has been accomplished in great part by the Public Health Service. While it would seem that sufficient warning had been given by the Service and other public health agencies so that the average citizen might be informed of the dangers offered by wild rabbits and some other animals, cases continue to occur in which no precautions have been taken. This is an excellent illustration of the cultural lag which occurs between the acquisition of valuable knowledge by scientists and the application of that knowledge by populations. Contrast this with the avidity with which radio was taken up by a large part of the population, when everyone from farm boy to professor was making his own set from 10-cent-store materials, and a lesson in human nature and in public health may be learned.

The Public Health Service had knowledge of 6,149 cases of tularaemia in the United States up to the end of 1935, with approximately 5 percent mortality. While this does not represent a major health problem, the fact that much of this distress and mortality could have been avoided by reasonable precautions renders the subject more interesting than the numbers imply.

The story of tularaemia has been so often and so well told that only a brief résumé of important Service contributions seems necessary here.

The first contribution came as a side issue to a routine job of examining thousands of wild rodents brought in from the field in California for the detection of plague foci, in the attempt to prevent human epidemics. McCoy was in charge of this work, which meant that he was doing a large part of it with his own hands. He was puzzled by the lesions which some ground squirrels exhibited. They had all the appearance of plague, but no plague bacilli could be demonstrated in them microscopically nor were inoculations into guinea pigs successful in showing the organism. Since both of these, especially the latter, were essential to a diagnosis of plague, McCoy had to ascribe these

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lesions to a "plague-like disease." Guinea pigs inoculated with these squirrel tissues died and showed lesions which any plague expert would pronounce highly suspicious, if not conclusive, but no plague bacilli were found. In his report (PHB 43, *1911*) McCoy shows that this infection was distributed through at least nine counties of California.

Cultivation of organisms could not be accomplished on ordinary media, and yet the infection could be destroyed by degrees of heat corresponding to the ordinary death point of bacteria, and filtrates of tissue were innocuous. The infection could be transmitted from squirrel to squirrel by means of fleas. Other rodents and monkeys were susceptible, but cats, dogs, and pigeons appeared to be resistant. The following year McCoy and Chapin reported the cultivation of the causative organism, to which they gave the name *Bacterium tularense* (PHB 53, *1912*). After trying various media they had at length grown the bacterium abundantly on coagulated egg yolk, and, now knowing what to look for, had found the organisms in infected tissues. The small Gram-negative rods, nonmotile and nonsporebearing, had a marked tendency to pleomorphism, and appeared as if surrounded by a capsule. A chronic type of infection was found in some guinea pigs which grossly resembled tuberculosis. Agglutination and complement fixation were manifested by antigens made from the bacteria with the serum from infected animals. The authors thought it likely that human beings would be susceptible. Of a number of supposedly normal human sera, two gave agglutination, which was not explained at the time, although 10 years later one of them was accounted for in retrospect as being due to an unrecognized infection (HLB 130, *1922*, p. 65).

And thus the matter rested, as an interesting infection of wild rodents likely to be confused with plague unless one were on the lookout for it, until Wherry, of the University of Cincinnati, demonstrated *B. tularense* in the lesions of two human cases of ulcerative conjunctivitis by means of guinea pig inoculation. Although human infections had been previously reported, this was the first bacteriological demonstration. Wherry also found the infection in two wild rabbits and issued a warning on the danger of dissecting such animals (RPHR 242, *1915*). Wayson reported the successful transfer of the infection by the bites of stable flies and by injecting crushed house flies or allowing them to crawl over abraded surfaces, the flies having had suitable exposure to infected materials (idem).

Again there was a pause in the accumulation of knowledge of tularaemia until Francis, at the request of the State health officer of Utah, was sent to that State to investigate what was locally called "deer fly fever" or the "Pahvant Valley plague." This he shortly identified as *B. tularense* infection conveyed to humans by the bites of

the "deer flies," *Chrysops discalis*, which had received it from diseased jack rabbits. He also discovered an epizootic due to this cause among jack rabbits (RPHR 555, *1919*).

A remarkable family outbreak was investigated by Freese of the Virginia State Board of Health and Lake and Francis of the Service, in which 4 members of a family became infected from eating imperfectly cooked rabbit meat, 3 of whom died. Some experiments were then conducted on the effect of cooking, and it was found that 10 minutes frying, involving the crisping of the outside, was insufficient to destroy the infectiveness of the juicy internal portion of a rabbit's thigh (RPHR 1064, *1926*).

Before this, Francis had examined 1,000 rabbits' carcasses held for sale at city markets and found 9 of them infected with tularaemia (PHR *1923*, p. 1391). Market men were found to be familiar with "rabbit fever" which was acquired by dressing wild rabbits.

Among the insect and arachnid transmitters of tularaemia was the wood tick. Parker, Spencer, and Francis showed that the bacterium could be transmitted in this tick from the egg stage up to the adult condition (PHR *1924*, p. 1057), and later Parker and Spencer completed the cycle through the egg to the next generation, thus adding evidence of the permanency of the infection among wild animals, since ticks could thus infect successive generations of small rodents (RPHR 1092, *1926*).

In a collection of articles Francis had shown that several additional insects and arachnids could transmit the infection, the horse fly, a rabbit louse, bedbug, and a mite of the mouse. He found that other media could be used for cultivation besides coagulated egg yolk, such as serum glucose agar, glucose blood agar, and blood agar, especially if pieces of sterile tissue were added. Cystine agar also was found suitable. In this collection he reported six cases of human laboratory infection (HLB 130, *1922*). The infection of laboratory workers is the universal experience wherever tularaemia has been worked with for any considerable time, especially where animal and insect experiments are carried out. It is idle to ascribe this to inexperience or faulty technique, except insofar as any technique for the continuous handling of animals and insects in this connection must be faulty. Bacteriologists and students should avoid experimenting with tularaemia unless called upon to do so in the line of duty. Similar infections have occurred at the Montana laboratory (RPHR 1090, *1926*), the plague laboratory at Los Angeles (RPHR 1091, *1926*), the Lister Institute, and elsewhere.

In the serological diagnosis of tularaemia some difficulty was encountered in the cross agglutination exhibited by this disease and undulant fever. It was found, however, that this could be overcome by considering the differences of titer, or if there were none, then by

agglutination absorption tests (Francis and Evans, RPHR 1089, *1926*). If opportunities for repeated tests are present, the increase of the specific one as the disease progresses is a differential point.

In RPHR 1191, *1927*, the seasonal prevalence of tularaemia was shown to vary with the manner of acquiring the infection. In the eastern sections, where there is an open hunting season for cotton tail rabbits during November, December, and January, the bulk of cases occurred during those months, since the infection was chiefly acquired by handling the diseased carcasses. In the West, where infection was received largely from jack rabbits, and the hunting was limited only by the weather or the uses to which the carcasses were put, the season was from April to October. Tick transference occurred during the tick season, March to August, while the deer-fly infections occurred from June to September.

Other publications refer to the susceptibility of various animals, coyotes, meadow mice, sheep, opossums, woodchucks, quail and partridges, etc., so that the list of possible sources is considerable, although rabbits still head it in great preponderance.

Since refrigeration of rabbit carcasses is now practiced for market purposes, Francis experimented on the effects of this agent and found that the infection nearly always remained active at a temperature of 3° C. for 1 month, and in one instance a carcass was infective after 5 months. No infection was found 6 months after exposure (AR *1931*, p. 66). Experiments at −15° C. showed that the infection might be retained for a year (AR *1932*, p. 61). It was shown by Lillie and Francis that this persistence might be attributed to the prevalence of the organisms in the bone marrow. The pathology of this structure was studied by them and the focal necrotic or granulomatous nature of the lesions described (RPHR 1593, *1933*). Francis has found that the spleens of guinea pigs which had tularaemia, preserved in glycerin at −15° C., retained their virulence for 10 years.

Tularaemia offers a striking example of the discovery of the causative organism before the human disease was known. In other words, the bacteriological investigation had been done when the disease was first recognized. It is also a valuable illustration of the useful results which may follow the investigation of the causes for the failure to get customary returns from routine experiments.

TYPHOID FEVER

Although Kinyoun was isolating the typhoid bacillus from stools of patients in 1889, in the little one-room Hygienic Laboratory of those days, and although, since that time, the Public Health Service has worked with this organism to an extent involving thousands of cultures, the actual bacteriological contributions of the Service to this subject have not been conspicuous. The reason is not far to seek.

Workable bacteriological methods were found ready at hand, and they were employed extensively by the Service in its noteworthy epidemiological studies and in its campaign against the disease.

In 1896 there was an epidemic of typhoid fever in Washington, D. C., and during an investigation sponsored by the local medical society and conducted by Dr. George M. Kober of that city, the Hygienic Laboratory performed all of the bacteriologic work, since the city health department had at that time no adequate laboratory facilities. Indeed, this service had been performed during the 2 preceding years.

In that same year the Service gathered statistics from United States cities situated on lakes and rivers, representing a total population of over 5,000,000, and found a death rate from typhoid fever of about 60 per 100,000, for the year 1895. Loss of life from this cause in the United States at that time is comparable to that from automobile accidents at the present writing.

In 1897 Andrade-Penny was working at the Hygienic Laboratory on his selective media for typhoid and confirming the value of the Widal tests on materials sent from the marine hospitals. He found Ehrlich's diazo-reaction of little value, since it was found in too many other conditions to be distinctive.

In 1898 Sprague continued the examination of the water supplies of the District of Columbia, which had been started in connection with the typhoid surveys, and he built up abundant evidence of the fecal contamination of both the shallow wells and the Potomac River water, sufficient to account for much of the typhoid fever which was then exacting a huge toll from the inhabitants of the Capital City.

During the several succeeding years there was much public agitation for a filtered water supply for the District of Columbia, which finally culminated in the installation of a well-appointed plant. To the consternation of the authorities, however, there was an actual increase in typhoid following the setting up of the filtration plant. This led to the appointment of a board of officers of the Service to study the prevalence and causes of typhoid fever in the District of Columbia. Consisting originally of Rosenau, Lumsden, and Kastle, it was enlarged later by the addition of Anderson. Kastle and Rosenau having resigned from the Service in 1909, Lumsden and Anderson completed the series of publications reporting the studies which had been made (HLB 35, *1907;* 44, *1907;* 52, *1909;* 78, *1911*). It is believed that these publications taken collectively represent one of the most valuable contributions which America has made to epidemiology. Their effects were far reaching, not only with regard to typhoid fever and its control, but also in the general field of epidemiology. During these studies a number of younger officers were trained in the methodology of the science and prepared for valuable service in connection with

many other diseases. Again, the Service was prepared by first-hand knowledge for the campaign which it shortly began against typhoid fever in the cities and rural districts throughout the country. Although there can be no claim that the general awakening of the country to the typhoid situation and the necessity for its control was solely due to these investigations, it is true that they and the subsequent campaign must have had a very considerable effect in this direction.

In passing, it may be of interest to note that Anderson and Perry, while investigating an outbreak in Lexington, Va., in 1904, succeeded in isolating the typhoid organism from the water supply, a feat which, although nonessential and in fact almost accidental, has not been accomplished very many times (AR *1904*, p. 381).

Field studies of typhoid outbreaks were made in many places by the graduates of the District of Columbia investigation, and a large experience was accumulated with the various forms of epidemics. Many times they were water-borne, sometimes milk-borne, often chiefly a carrier proposition, and a few times they were of shellfish origin. Of course these studies always involved a bacteriological check-up.

By 1911 the Service campaign against typhoid was well under way. Lumsden was finding that the way to rural control lay in the establishment of county or regional health organizations on a full-time basis, an activity that has progressed favorably from that time to the present, so that the time may be envisioned when the rural dweller may have as good a chance of avoiding preventable infections as his city cousin. At the same time, McLaughlin was making his sanitary surveys of cities using surface water, and preaching the gospel of sewage disposal and water purification. Important though these activities were, they do not belong strictly in the field of bacteriology, although that science was constantly acting as the handmaiden of the sanitary arts.

The stream pollution studies of the Service (see chapter on Water) and the milk studies (p. 36) were, of course, largely concerned with typhoid fever and had their effect in its conquest.

In the registration area of the United States the typhoid death rate had declined from 35.9 per 100,000 in 1900 to 5.5 per 100,000 in 1928. The larger American cities at least had reduced their death rates to 1, 2, or 3 per 100,000. Nevertheless, how narrow the margin of safety still remained was illustrated in 1927 by the tragic experience of Montreal, just across the Canadian border, where there were some 5,000 cases with the usual 10 percent of deaths. This was a milk-borne outbreak. An investigation by Service officers, permitted on account of the international hazard, revealed that supposedly pasteurized milk was not such in fact, and emphasized the need for supervision of the milk industry by health authorities.

Of some interest to bacteriologists is the isolation from a mild enteric case, at first thought to be typhoid fever, of an apparently new organism, *Alkaligenes fecalis radicans*, by Dr. Evans (RPHR 1493, *1931*).

TYPHUS FEVER

It is believed that the discussion to follow would be clarified by some preliminary statements summarizing the present beliefs of Public Health Service workers in typhus fever. These will concern the question of definition for the most part. It appears that there are scattered over different parts of the world a number of similar diseases, differing slightly from each other in one or another particular, but resembling the type form, European exanthematic typhus, in general characteristics, prominent among which is a cutaneous eruption which tends to become petechial. In the United States there are, or have been, three well recognized forms of this infection: Rocky Mountain spotted fever (including its eastern form), which, however, is marked off by immunological considerations from the others and has been discussed under its own heading; epidemic typhus fever, a louse-borne disease readily transmitted from man to man, and hence capable of causing extensive outbreaks; and endemic typhus fever, transmitted by fleas, perpetuated in rats, and causing isolated, unassociated infections in men. It is only fair to note that some observers believe these last two forms to be identical, and that their manifestations vary only with the vector, louse or flea, which happens to be concerned in a given case. However this may ultimately prove to work out, the Service prefers at present to think of epidemic typhus as identical with the historic Old World disease, the same as the louse-borne typhus of the Mexican uplands and which was responsible for early epidemics in some American cities.

Epidemic typhus.—The last considerable outbreak of this disease on American soil is believed to be that of 1920–21 among the Navajo Indians on a reservation in Arizona and neighboring States. This was definitely louse-borne, involved 63 cases with 27 deaths, and was controlled by antilouse procedures carried out under great difficulties (Armstrong, PHR *1922*, p. 685).

Epidemic typhus, aside from this outbreak, has been studied by Service officers in Mexico and by means of viruses secured from Europe. In Mexico, in 1909, 1910, and 1912, Anderson and Goldberger transmitted the local form by means of human blood to monkeys, and determined that the virus was not filterable. They were able finally to infect monkeys by louse bites and by the injection of crushed lice. In addition to the body louse they adduced evidence that the head louse could transmit the disease (PHR *1909*, p. 1941, *1910*, p. 177, *1912*, p. 297). Attention being directed about this time to Brill's disease, a strain of

which was being carried along at the Hygienic Laboratory, cross immunity experiments were made in Mexico with monkeys inoculated with the New York virus, and complete cross immunity in both directions was shown, so that as regards this criterion the two diseases are identical (HLB 86, *1912*). A differential point was introduced by Neill in 1917, consisting of scrotal lesions in guinea pigs, but this appears to be a quantitative rather than a qualitative distinction (RPHR 409, *1917*).

Endemic typhus.—At the present time, according to Service views, there is but one type of typhus fever in the United States if we exclude Rocky Mountain fever from this category on the grounds of its failure to produce cross immunity. This is known as endemic typhus because it occurs in isolated cases, is not transmitted from man to man, and two cases in the same house are of extreme rarity. This is believed to be identical with the disease described by Brill, in 1915, as a mild type of typhus and as early as 1898 as a typhoidlike disease giving no Widal reaction.

Beginning about 1913 a few cases of mild typhus began to be reported by observers outside the Service in different parts of the Southern States, and 10 years later Maxcy, of the Service, whose duties brought him into these areas, began to be impressed with the rather considerable total incidence of such cases. After some preliminary publications Maxcy, in 1926, reported on 114 cases in the Southern States, and succeeded in transmitting the disease to a monkey and guinea pigs (PHR *1926*, pp. 1213 and 2927). He is chiefly responsible for bringing this infection to the attention of health officials and making the first observations on its essential epidemiological features. Chief among these are the facts that this southern form predominates during the latter half of the year, and among persons who spend much time in the neighborhood of markets or other places infested with rats. He inferred a rat or mouse harborage of the virus and the infection of man from rodents by means of ectoparasites. A striking feature of the disease as observed by him was the absence of louse infestation of the patients, contrasting in this respect with the traditional history of typhus fever, but corresponding to the experience with Brill's disease.

The next phase of the researches of the Service on endemic typhus was the proof of Maxcy's inferences. He himself showed that the virus of endemic typhus could infect white rats. It produced some symptoms in them, and the virus could be demonstrated by guinea pig inoculation of the brain following intraperitoneal inoculation of the rats, and rickettsialike bodies were found in the tunica vaginalis (RPHR 1305, *1929*). Dyer, Rumreich, and Badger adduced the next evidence. Rats were trapped at a focus where human infections had been acquired, and guinea pigs were infected by means of fleas taken

from these rats (RPHR 1448, *1931*). Then it was shown that infection could be transmitted from rat to rat by the flea *Xenopsylla cheopis* (RPHR 1520, *1931*). That the flea transmits the disease through its feces which become rubbed into the wound, rather than by the act of biting, was indicated by the experience reported in RPHR 1524, *1931* and 1525, *1932*. It was shown also that fleas may remain infective for at least 52 days, a sufficient time to permit their infection of successive crops of rats. While it was shown (RPHR 1531, *1932*) that another flea, *Ceratophyllus fasciata*, could transmit the virus, other evidence indicates that *cheopis* is the important vector in nature. An enormous multiplication of the virus in the body of the flea is shown by the titration experiments reported in RPHR 1532, *1932*. The criteria for the recognition of the virus of endemic typhus established by these workers (Workman, Lillie, and Ceder participated in some of the experiments) are, briefly, that it must produce typical temperature and scrotal reactions in guinea pigs, and histological lesions in their brains as well as Rickettsiae in the tunica. Recovered animals must be immune to known strains, and those recovered from known strains immune to the virus. Rabbits treated with the virus must develop agglutinins to *Proteus* X19 type O. Blood cultures must exhibit no growth. The adherence to these criteria is necessitated by the fact that intercurrent infection, especially by a *Salmonella enteritidis*, may confuse the issue unless ruled out.

The final link in the chain of evidence was the finding of the infection in a wild rat taken from a focus of human infection (RPHR 1558, *1932*). This, however, had been independently accomplished.

From this work on endemic typhus the conception emerges that there is a rickettsial disease of rats, probably not very lethal to them, maintained among them by fleas, and communicated occasionally to persons, chiefly those who frequent rat-infested neighborhoods, such as the wholesale districts of cities. This is distributed chiefly among the Atlantic seaboard and the Southern States so far as we know at present. At least for public health purposes it is to be distinguished from the Old World type of louse-borne typhus, and there is some evidence that the viruses differ in some particulars. It seems probable also that this disease is not transmitted by the flea during the act of biting, but rather from the rubbing of the flea feces into wounds or abrasions made during scratching.

VENEREAL DISEASES

When it is reflected that for some 140 years the Public Health Service has been giving medical relief to sailors of the merchant marine, it will be understood that it has accumulated some experience with the venereal diseases. While there are contributions on the sub-

ject from the pens of a number of medical officers during the early and pretreponemal days, they naturally have no bacteriological significance. Nevertheless, that the scientific spirit was not wanting is evidenced by an article by H. R. Carter (AR *1885*, p. 131) in which he draws the conclusion that the manifestations of syphilis are in general milder in the colored than in the white race. He has reference to the external manifestations, and it may well be doubted whether the conclusion is correct if the end results are considered. The interest of the article resides in the painstaking methods of recording and analyzing the data, which were collected on 231 cases in each group, white and colored. Such methods were not conspicuously prevalent in the medical literature of the time.

Attempts were made by several officers to estimate the prevalence of these diseases. Thus Banks (RPHR 262, *1915*) tried to apply the figures obtained at marine hospitals to the general population, making what appeared to him the necessary allowances for various factors. He concluded that there were nearly 2½ million cases in the United States each year, although less than 3 percent acquired the infections (all forms) annually. Bryan and Hooker compiled the data on admissions at one marine hospital and found that 28.2 percent of the patients admitted had syphilis as shown by clinical signs or by the Wassermann test. Such figures would have greatly augmented Bank's estimate for the general population (RPHR 378, *1916*). Following the establishment of the Venereal Disease Division in the Service (1918), a number of attempts were made in cooperation with other agencies to estimate prevalence, chiefly by means of the 1-day survey method, in which the endeavor was made to ascertain from the reports of physicians and clinics all the cases under treatment for syphilis or gonorrhea in a given territory on a single day of the year. The 1935 survey estimated 518,000 new cases of syphilis and 1,550,000 of gonorrhea acquired annually in the United States, these constituting 20 percent of all communicable diseases (AR *1935*, p. 12).

This represents a vast public health problem on which, despite its magnitude and complexity, the present Surgeon General, Dr. Thomas Parran, is conducting a determined and comprehensive attack, utilizing the resources of the Service in cooperation with all helpful agencies. Despite the somewhat discouraging outlook, there are a number of factors which, at first glance, would place the worker in venereal disease prevention in an enviable position. The specific causes and methods of transmission are known. There are specific laboratory aids to diagnosis. And there are (in the case of syphilis) specific methods of treatment effective at least in rendering treated persons much less liable to convey infection. There are,

moreover, susceptible experimental animals on which certain forms of research may be conducted. Such information and facilities form the goal toward which infinite research is striving as yet unsuccessfully with regard to many another communicable disease.

The essentials of the above items of information were furnished by Schaudinn, Ehrlich, and Wassermann as regards syphilis, and subsequent work has been merely in the direction of refinement. In a symposium on research in syphilis (VDI *1928*, p. 525) the desiderata from the clinical, laboratory, and public health viewpoints were set forth by Moore of Johns Hopkins, Brown of the Rockefeller Institute, and Parran of the Public Health Service, respectively.

To some of these, workers in the Service have addressed themselves. The arsenical drugs used in the treatment of syphilis were interpreted by a ruling as coming under the Biologics Control Act, and this led to a large amount of research of a chemical and chemotherapeutic nature. Work on the toxicity of arsenicals is reported in HLB 128, *1921*. Little of this work, however, has a very direct bearing on bacteriology. *Trypanosomes* were at one time thought to be useful as test organisms for the potency of these arsenicals, because inexpensive laboratory animals may readily be infected with them. However, there appeared to be no constant correlation between the action of these drugs upon these organisms and the causative organism of syphilis. Moreover, *trypanosomes* are prone to become arsenic-fast. This property again may be unequal as regards various preparations, such as arsphenamine and neoarsphenamine (Lake and Probey, RPHR 843, *1923*).

Studies with various forms of the complement fixation test were carried out (at the Hygienic Laboratory) at an early period in the history of these reactions, all of the reagents being investigated as fundamentally as the science of the day permitted, and a standard technique was devised for the institution. This was published later by Neill (RPHR 483, *1918*), and the method was introduced as far as practically possible throughout the hospitals of the Service, standardized reagents being shipped to them. Many attempts have been made from time to time to secure the adoption of standardized methods throughout the country. It has been the almost universal experience, in conferences for this purpose, that each participant was entirely favorable to the plan, provided his own technique be adopted. The bulk of the complement fixation tests for the entire Service, including a large number performed for the Department of Justice, are now done at the National Institute of Health, amounting to some 30,000 specimens annually. The Kahn test also is done on all specimens. The application of the latter test to experimental animals was investigated by Mahoney and Bryant. Despite the high prevalence of positive reactions in normal rabbits they thought the test useful

for recording serological changes in these animals (RVDI 23, *1930*) following testicular inoculation. Guinea pigs nearly always give a completely negative reaction which is not altered by attempts at inoculation (RVDI 33, *1931*).

The question of the persistence of living spirochetes at various stages of syphilis in man, both in treated and untreated persons, has important medical and public health bearings. Lake and Bryant applied the technique of lymph gland transfer to rabbits to this problem. Sixty-six cases, divided into various categories as regards duration and treatment, were studied by this method. While successful transfers of the treponemata were secured in all 34 early untreated cases, and in 4 out of 9 cases of long duration but inadequately treated, on the whole the method was considered inadequate for the solution of all problems involved (NIHB 157, *1930*).

Bearing importantly upon the success or failure of methods of individual prophylaxis after exposure is the time factor. Previous animal experimentation had made use of scarification to favor the ingress of the organisms, which probably does not copy the usual method of human infection. Mahoney and Bryant, therefore, experimented on the penetration of the rabbit genital mucosa without scarification and found that it occurred in 3 hours after application of the inoculum. After this time applications of iodine or alcohol were only partially effective, although they gave complete protection after 2 hours. Cleansing with white soap was only partially effective when applied after 2 hours, and was useless after 3 hours.

The Service participated in 1935 in the work of a committee which considered the comparative value of fixation and flocculation tests. The conclusions were that the two procedures had equal value. Instead of more cumbrous methods of reporting results, they recommended that they be reported simply as positive, doubtful, or negative (RVDI 52, *1935*).

It is believed that a considerable advance in the facility of early diagnosis has been made possible by the method of shipment of specimens for dark-field examination elaborated by Mahoney and Bryant (VDI, Mar. 20, *1930*).

One of the most valuable functions of the Division of Venereal Diseases of the Service is the publication of the monthly bulletin Venereal Disease Information. Containing as it does timely special articles, and a very complete review of the world literature, it would seem that no specialists in venereal disease could well get along without access to it.

WATER

Early studies.—The dissemination of disease through drinking water has been a matter of major interest to the Public Health Serv-

ice for more than 40 years. It is believed that the Service has played an important part in bringing about the remarkable reduction in such diseases during that time. Its efforts have been dual in nature; first, in studying the physical phenomena of stream pollution and purification in all its phases, and, second, in emphatically bringing to the attention of health officials the prevalence of water-borne diseases and in assisting them in the application of remedies.

Soon after the establishment of the Hygienic Laboratory in 1887, workers there became familiar with the typhoid bacillus and other water-borne organisms. Kinyoun isolated the typhoid bacillus from stools in 1899. In 1894 and 1895 the Hygienic Laboratory performed all of the bacteriological work incident to investigations into the prevalence of typhoid fever in the District of Columbia inaugurated by the local medical society. A high degree of pollution of wells, springs, and the Potomac River water was shown (AR *1896*, pp. 1008 and 1009). Continuing these examinations, by 1898 the Service had secured data upon the river water well up toward the source, and frequent instances of serious pollution were encountered. Much of the bacteriological work was performed by Passed Asst. Surg. E. K. Sprague (AR *1898*, pp. 810–813). It will be recalled that this was at the period of the terrible losses among United States troops from typhoid fever at the camps and in the field.

In response to an effort to determine the prevalence of typhoid fever throughout the country, begun by Surgeon General Wyman, statistics gathered in 1896 from cities located on lakes and rivers, totaling over 5,000,000 inhabitants, showed that during the preceding year 3,050 deaths had occurred, making a death rate from this one disease of about 60 per 100,000.

In the meantime the system of water purification already employed in some European cities had been investigated and reported upon by Service officers. Rosenau reported on the Anderson system which had been installed at Antwerp in 1865 (AR *1893*, II, p. 166), Kinyoun studied the filtration system at Hamburg in 1894, and in 1901 Geddings published an article comparing the mechanical and slow sand methods (AR *1901*, p. 610).

In ensuing years the Service acquired increasing knowledge both of water bacteriology and of water-borne disease through the investigations of frequent epidemics which it was called upon to study.

As a result of country-wide agitation, filtration plants were now being installed in various American cities. One was placed in operation in the District of Columbia, but as previously noted, to the surprise and chagrin of health authorities, typhoid fever actually increased during the first years following its installation, although by all tests it appeared to be operating properly. This situation led

to the appointment of a board to study typhoid fever in the District, consisting of Drs. Rosenau and Lumsden and Professor Kastle, officers of the Public Health Service. The labors and reports of this board, which it is believed constitute one of the most significant American contributions to epidemiology, are described in the chapter on typhoid fever.

Common carriers.—In 1908 the question of controlling the water supplies on common carriers was taken up by the Public Health Service. Since many trains and steamboats engage in interstate traffic, they would come under the control of the Federal Government. Instances were known of outbreaks due to polluted water served on such carriers. The energetic prosecution of this activity from that time up to the present has resulted not only in the protection of the traveling public but in unforeseen improvements in water supplies throughout the land. It became necessary early in the exercise of this control to define certain minimum standards of sanitary quality which would be satisfactory if complied with. These included a bacteriological standard, and this in turn involved a great many bacteriological determinations. The State health departments were called upon to furnish many of the latter which in the nature of the case could only be made within reasonable shipping distances of the sources. In order to comply with the request many of the State health departments were obliged to increase their personnel and facilities, which in truth was in many instances much to be desired for other reasons. It was then found in a good many cases that the improved and corrected supplies for common carriers were superior to those of important cities within the States. The need for improvement of the latter was thus emphasized and in general supplied. In not a few cases the building up of an adequate State sanitary engineering service with its accompanying bacteriological facilities may be said to date from the inauguration of this activity. The question of furnishing a safe water supply to travelers on trains and steamboats is not a simple one. After surveys and laboratory tests have shown the source to be satisfactory, there remain to be solved the important problems of transferring, refrigerating, and purveying. The work in this connection carried out by the Service would fill several chapters of practical bacteriology combined with sanitary engineering. In steamboats especially, the complicated piping systems afforded plenty of occupation for Service engineers. Many cross connections were found which would have had the effect of serving diluted sewage to the passengers on occasion.

Interstate streams.—In 1909 an unsuccessful attempt was made to secure legislation to bring interstate and international waterways

under the sanitary control of the Government. In the absence of specific authority, however, fairly satisfactory arrangements have been made by reciprocal agreements between State health officials, and these have been fostered in some cases by the Public Health Service. In some of these the Service has undertaken a portion of the survey or laboratory work essential to a solution of the problems presented.

International waterways.—In 1913 laboratories were established by the Service at Buffalo and Detroit for water examinations incidental to the work of the International Joint Commission established in that year by this country and Canada. The Service was represented on this commission by Dr. A. J. McLaughlin in the capacity of chief sanitary expert and director of field work (AR *1913*, p. 42). The labors of this commission have been very successful in laying the basis for the prevention and settlement of such sanitary questions regarding international waterways as might arise.

The Cincinnati laboratory.—In July 1913, the Service opened a laboratory in the marine hospital building at Cincinnati (no longer required for hospital purposes) which was to be devoted exclusively to the study of streams used for water supplies, as regards their pollution by human wastes and their purification by natural and artificial means. This activity was placed under the general direction of Surg. W. H. Frost, who continued to serve in this capacity for many years and is largely responsible, along with his capable associates, for the high quality of the scientific work achieved. A group of specialists was stationed at the laboratory to make a well-balanced working unit, in which sanitary engineering, bacteriology, chemistry, and planktonology were ably represented by such men as Hoskins, Crohurst, Streeter, Butterfield, Theriault, and Purdy.

Except for a few years during and following the World War, the activities of this laboratory have been continued and amply supported, and it is believed that they have constituted one of the best investments not only of the Public Health Service but of the Nation. The importance of the knowledge which they have developed can be appreciated only when it is realized that some 80 percent of our population gets its water supply from surface or river waters, and that in many cases the same water is necessarily used repeatedly, with interpolated purifications, by successive communities. The problems, in brief, with which the station was to concern itself were as follows: The extent and nature of pollution of streams, to what extent natural processes could be relied upon to effect purification, how much remained to be taken care of by artificial means, and what methods should be employed to effect such purification.

Potomac River study.—In addition to the early surveys of the Potomac River already referred to, the Service during 1913 and 1914 made a more elaborate study of that river (HLB 104, *1916*). Dr. H. S. Cumming, afterwards Surgeon General, was in charge. The study included a sanitary survey of the entire watershed with the collection of data on the prevalence of typhoid fever and the existence of manufacturing wastes, hydrographic studies of stream and tide flow, a study of shellfish culture in the lower reaches, and numerous bacteriologic and chemical determinations made at various stations established along the course of the stream. In this way certain sanitary characteristics of a stream of this nature were established. Scientifically, perhaps the most interesting result of the study was the demonstration of the remarkable purification effected by certain shallow bays connected with the river, whose prolific growth of water plants furnished an abundance of oxygen to the polluted water during its overflowing of the areas at high tide. This natural process was compared, by Prof. E. B. Phelps who was associated with the survey in his capacity as Chief of Chemistry at the Hygienic Laboratory, to the purifying action of the lungs upon the blood in animal physiology. But the Potomac after all represents only one type of stream and cannot be considered typical of the majority of those supplying the American public. It may be described as a relatively rapid stream, traversing hilly and not heavily inhabited areas, with rather small industrial contamination, supplying few and remote communities with water, and spreading out in its lower part into a tidal and increasingly saline estuary where, still farther down, shellfish are commercially cultivated.

Ohio and other rivers studied at Cincinnati.—By contrast, the Ohio River, for example, is a relatively slow stream with numerous tributaries draining a densely inhabited and largely industrial terrain having numerous cities along its banks which deliver an enormous load of sewage and manufacturing waste, and in which the problems of both natural and artificial purification are entirely different. The Ohio River was selected as the first subject of study by the Cincinnati laboratory, while at the same time it carried on fundamental biological and chemical studies suggested by the findings which poured in from the subsidiary laboratories, and from the water purification and sewage disposal plants along the course of the stream. In the course of these studies it became expedient to construct on the laboratory grounds a filtration plant in miniature, so connected that processes could be applied in any desired sequence and to any desired concentration of pollution, and where conditions could be controlled for scientific study better than in any municipal plant in actual operation. The findings made in the field were checked against those of

this plant and certain fundamental formulae arrived at which could be used for future guidance of those in charge of such municipal plants. A description of this experimental plant and its operations will be found in RPHR 1114, *1926*. Other experimental studies are found in RPHR 1317, *1929*, 1328, *1929*, and 1336, *1929*.

Another device intended to simplify the natural purification problem by eliminating many of the uncontrollable complications encountered in natural streams, in other words, to reduce the factors to lowest terms, consisted of an artificial river nearly a mile long which was set up on the laboratory grounds. This was a shallow channel set up on posts so that the desired rapidity of flow could be secured. Water of any chosen degree of pollution could then be run through these channels and samples taken for examination at any point in their course. The writer remembers the clean-cut periodic changes in the appearance of the water and its bed which a mere inspection could determine, such as the sharp disappearance of the shaggy gray algae of the upper reaches, and the equally sharp appearance of blue-green algae in the lower. The structure was subsequently enclosed in glass so that observations could be made throughout the entire year and the influence of temperature computed. Many thousands of tests were made on samples from this artificial stream, including bacteriological, chemical, and plankton determinations, and in the light of the coordinated findings the processes occurring in natural streams were more intelligently interpreted.

Along with these experimental studies two other lines of work were carried out. One consisted of intensive studies of rivers, the other of actual water treatment plants in operation. The Ohio River was twice studied, once before and again after its canalization, which practically made a different stream of it from a sanitary standpoint. Then came the Illinois River and certain stretches of the Mississippi. A variant presenting a different order of problems was presented by studies of the lower end of Lake Michigan. It is impossible here to review the scientific facts brought out by these studies. Suffice it to say that the publications emanating from this office have taken high rank in the world literature of the subjects with which they deal, have been employed in teaching in schools of public health and engineering, and that the writer observed complete sets of them, well thumbed, on office shelves at filtration plants in remote parts of England. The first two Ohio River reports are found in PHB 131 and 143 published in 1924 (see also PHB 146). A summary in the Annual Report of the Surgeon General for 1924 states that the decrease in bacteria in both the Ohio and Illinois Rivers follows a definite and orderly course conforming approximately to fairly simple mathematical formulae. It was, of course,

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toward the establishment of such formulae that the whole work was directed, general laws which, when the conditions in any stream had been determined by a relatively simple survey, could be applied for the prediction of conditions which would obtain under the various changes of load, stream flow, and temperature to which streams are subject.

By 1926 (AR *1926*, p. 4) it could be stated that—

> studies in stream pollution * * * have succeeded during the year in laying the basis for impartial settlement of an interstate situation before it assumed the nature of controversy.

In 1926 (RPHR 1063) Dr. Frost published a review of the work of the Public Service in investigation of stream pollution.

Filtration plant efficiency.—The other principal study, that of the operation of filtration plants, conducted by Sanitary Engineer Streeter, was so planned that some 15 municipal plants, having various problems and methods of meeting them, were induced to adopt a uniform method of testing and recording (RPHR 927, *1926*). A report on the efficiency of these plants is found in PHB 172, *1927* and PHB 193, *1929*, and of methods proposed to increase it in RPHR 1114, *1926*, and 1170, *1927*. Naturally, through a comparison of methods and results thus furnished, not only were these particular plants enabled to adopt the most advantageous methods, but plants throughout the country generally could profit by the accurately recorded experience.

Coagulants.—A subject of much importance to filtration plants and to the cities employing them is that of coagulants. Alum is most commonly employed. While alum is cheap by the pound if a little is needed for household purposes, the city bill for tons of the substance is no small item. In 1922 (AR *1922*, p. 77) it was shown at the Hygienic Laboratory that the effective floc produced by alum in potable waters is dependent upon the hydrogen-ion concentration. Equations were derived for a range of concentrations. The writer has vivid recollections of his efforts to explain pH to an appropriations committee, and what that had to do with public health. While the point about the reciprocal of a logarithm may not have been fully appreciated, although it is impressive, the main fact that it saved lots of money was duly applauded. Of course, by a simple determination of the pH of the water, plant operators could now determine just how much alum to add in order to get maximum results, instead of dumping in several times too much in order to "make sure." This is just one of the ramifications of the work of Wm. M. Clark, at that time Chief of the Division of Chemistry at the Hygienic Laboratory (PHR *1923*, p. 181). The subject of coagulants,

of course, received much further study at the Cincinnati laboratory (RPHR 992, *1925*, and 1023, *1925*).

The working unit at Cincinnati has been highly successful and productive. It is not always that a planned and organized research succeeds. Many times the brilliant independent worker with a few test tubes and an idea slips in ahead of the cumbrous organization. Success in this case seems to have been dependent upon an almost ideal set of circumstances. In Frost, the unit had a leader and critic possessing a broad grasp of the essential problems and bringing rigid scientific scrutiny to bear upon all results. The unit was particularly fortunate also in its board of consultants, among whom were such men as Stephen A. Forbes, E. O. Jordan, Langdon Pearse, E. B. Phelps, and Joseph W. Ellms. The working personnel also, which has changed little during the years, each able in his own specialty, were able congenially to focus the methods of several different scientific disciplines upon the problem. And finally, which is not always the case in research work, the problem, granted hard work and persistence, was not insoluble.

Ground-water studies.—Before leaving the subject of water, reference must be made to a very unique experiment conducted over several years at Fort Caswell near Wilmington, N. C., by Dr. C. W. Stiles and Sanitary Engineer Crohurst, with a small bacteriological staff. This was a study of ground-water pollution. Pettenkofer would have enjoyed it and profited by it. In essence it consisted of the measurement of the progress of pollution placed in pits in the sand as it followed the ground-water table in a horizontal direction, while its depth also could be determined. This was accomplished by an ingenious arrangement of "wells," consisting merely of small caliber tubing thrust into the ground at various distances and depths, and having a suction apparatus at the top by means of which specimens of water could be drawn out for examination. The results were most interesting and, perhaps, unexpected. After 27 weeks, for example, the pollution had spread 115 feet horizontally, and was found to occur only in the surface of the zone of saturation in a thin sheet. It was followed further and further under various conditions of drought or rainfall, and its final results are to be found in HLB 147 published in 1927, some 5 years after the beginning of the work. The only criticism (if it is such) of this work which occurs to me is that it almost amounts to pure research. It certainly establishes accurately and for all time the rate and level at which fecal pollution spreads in a medium composed of sand having a subsurface ground-water table. This should apparently be the starting point for the solution of a great many sanitary problems. Unfortunately, however, the majority of problems involving ground pollution deal

with a heterogeneous medium composed of sand, rocks, humus, clay, and other material. Obviously we cannot apply the results of this pure research to such media. Like Euclidian geometry, which also deals with an idealized medium, this research has both its uses and its limitations.

A narrow margin of safety.—It will be remembered that, at the beginning of the century, the death rate from typhoid fever in American cities was enormously and disgracefully high. Then came the filtration plants and the remarkable reduction of all water-borne diseases. There remained, however, a residue of typhoid fever. In 1928, Dr. Veldee was sent to the Ohio River cities to endeavor to assign a cause for these residual cases. His studies indicated that there was no reason to ascribe any of these to the failure of any public water supply. It appears that high bacteriological standards will, if maintained, afford absolute protection. On the other hand, all of these river studies have shown that the permissible degree of pollution of many of our streams has just about been reached and that the margin of safety is not a broad one. It was stated (AR *1930*, p. 64) that the average well-operated rapid sand filter plant with subsequent chlorination can produce a satisfactory effluent if the average *B. coli* index does not exceed about 5,000 per 100 cc and that with certain elaborations somewhat higher pollutions can be cared for. There are, therefore, definite limits to the possibilities of purification by known methods. With the increase of population and industry, a future menace is apparent. This has turned the attention of the Service back again to the possibilities of improving sewage disposal.

YELLOW FEVER

Yellow fever was familiar to officers of the Marine Hospital Service previous to its reorganization, as a visitation which they encountered in their tours of duty at Atlantic and Gulf coast stations and on the Mississippi River. They witnessed it, diagnosed it on clinical evidence, treated it, some of them contracted it, and a few died of it. It was, however, a medical rather than a public health problem with them until after the reorganization of the Service in 1870, and especially after the quarantine acts of 1890 and 1893, when it became a responsibility and a nightmare. A list prepared by the Service (AR *1895*, p. 428) indicates that the disease first occurred on American soil in 1668, that outbreaks were frequent during the eighteenth century, and never absent during the nineteenth for more than 2 or 3 years, up to the completion of the list in 1893. Following the acts referred to, the responsibility was definitely laid upon the Service of keeping the disease out of the country and of preventing its spread in case of introduction or recurrence. In complete ignorance

concerning the cause or transmission of the scourge, officers detailed to this duty worked heroically, if blindly. At the quarantine stations they dipped ballast in bichloride solution and fumigated holds with sulphur. They plunged into infected cities verifying diagnoses, treating the sick, and trying to bring order out of chaos. They established sanitary cordons around infected areas, and, really significant, they set up detention camps at a distance of a few miles, clean, well-managed, on quasi-military lines, where refugees could remain for the period of incubation, and could be fed and housed and kept under medical surveillance until they were permitted to pass on to the safety of uninfected territory. Most of these officers were too exhaustingly busy to do more than get through with the day's work, but a few found time to take notes and to speculate as to causes.

Even as early as 1875 Surgeon Vansant concluded, as a result of his observations, that the cause of yellow fever must be "a solid, or semisolid, endowed with life" (AR *1875*, p. 149). In the following year Asst. Surg. Henry Smith recorded his belief that the morbific element "exists in living germs propagated without the body, but which can be studied only by their effects on the human organism" (AR *1876–7*). As a practical epidemiological procedure Dr. John Guiteras, while acting as a sanitary inspector for the Service, suggested as means of detecting yellow fever outbreaks, that the death records of the suspected locality be examined and that any recent unusual preponderance of deaths among white persons, especially children and natives of northern States or of Europe, should be considered indicative of the presence of yellow fever. As is well known, local authorities were prone to doubt or conceal this disease, especially at its beginning, and the doctors frequently made errors of diagnosis, the most common, according to Guiteras, being to attribute these early cases to acute cerebral or gastroenteric affections, and, above, all to acute manifestations of malaria (AR *1894*, p. 298).

Among the most indefatigable workers, note takers, and thinkers, was Dr. Henry R. Carter, a man whose intellect would take front rank in any assemblage. His approach to the yellow fever problem was the solid one of accurate observation and meticulous recording, followed by rigid analysis. It was years before this method began to bear fruit. One can trace its progress through his official reports and articles. There was nothing speculative in his methods. Everything was factual, with names, dates, and places given. His epidemiological deductions foretold with remarkable accuracy the conclusions which were subsequently reached by the Army commission in its epochal experiments. Taking as his unit for discussion the house or residence, Carter concluded that a person sick with yellow fever need inhabit a house only a short time (less than 24 hours) in order to infect the premises; that this house, although infected,

could not transmit infection to persons until the lapse of about 2 weeks; that other persons living in the house but not otherwise subject to exposure, escaped the infection if they removed to "clean" surroundings within about 10 days, but that, if they remained much over 10 days they came down with the disease, and that within a short time of each other—"in a bunch"; similarly, visitors to the house within the first few days of illness of the first patient did not become sick, while those visiting there during the third week became infected; that disinfection (fumigation) was effective in preventing new cases if done early in the case of the first patient. Dr. Carter remarks in one of his articles, published after the Army commission's report, that their period of extrinsic incubation was somewhat longer than that indicated by his series. In view of the fact that human experimentation can even at this time not have reached numbers approaching those in Carter's series, it may well be that his epidemiological data still represent a more accurate determination of the possible limits. In the various reports of Major Reed and his coworkers, acknowledgment is made of the accuracy and value of Dr. Carter's contributions (Yellow Fever, Senate Document 822, *1911*, pp. 9, 59, 120). Unfortunately, epidemiological data never can carry the weight of experimental demonstration; we are always afraid of some slip in the observations or the logic, and we rarely have a Carter to furnish both. Dr. Carter's essential contributions to this phase of yellow fever are found in AR *1900*, p. 230, p. 242 and Med. Rec., *1901*, **59**: 361.

Sharing the general acceptance of the mosquito theory following the demonstrations in Cuba, the Service quickly adopted and perfected methods of prevention and control based upon its principles.

While in the hands of Carter the methods of epidemiology were surely approaching the solution of the yellow fever mystery, bacteriological work relating to this disease in the Service and elsewhere was going sadly awry. Geddings and Wasdin (AR *1899*, p. 861) thought that they had completed Koch's cycle with regard to Sanarelli's *B. icteroides*, and convinced themselves, but probably few others in the Service or elsewhere, that this was the etiological agent. Currie (AR *1901*, p. 601) furnished them with a control series showing that *B. icteroides* could not be found in ordinary hospital cases. Proust and Wurtz, at the Congress of Hygiene and Demography in 1900, reported favorably without protest on Sanarelli's germ, and even Agramonte before joining the Army commission had isolated it from about a third of a series of yellow fever cases. Such mistakes are not rare in bacteriology (witness, for example, the hog cholera bacillus, and Nocard's bacillus of psittacosis) and will probably occur again. Possibly an analysis of the source of these errors

would be profitable in preventing future ones. It would be flippant to dismiss the matter with the dictum that these workers were just "seeing things."

During the New Orleans epidemic of 1905, tissues were secured at autopsies, preserved in various ways, and sent to the Hygienic Laboratory for future study. In only one of the few of these which had been preserved in formalin were spirochetes found in the kidney in large numbers by silver impregnation methods. The finding was reported as of possible interest (PHR *1907*, p. 541) and the name *Spirochaeta interrogans* was suggested on account of the question-mark-like curve of one of the ends. The organism proved later to be identical morphologically with Noguchi's *Leptospira icteroides*, now known under the name of *Leptospira icterohemorrhagiae* as the cause of Weil's disease. Apparently by a mistake quite natural during the course of an epidemic, tissues from a case of hemorrhagic jaundice had been included among the yellow fever specimens. This is rendered more probable by the statement on the bottle that the patient had died during a relapse.

While yellow fever has apparently been demonstrated not to be a bacterial disease, there were many claims to the discovery of bacterial agents during the early years of study of the disease. Some of these were investigated by the Service. Thus, a claim by Dr. Carlos Finlay, published in 1887, was tested by Kinyoun in 1889 at the New York laboratory and no support was afforded. Possibly this result led later to a lack of confidence in Finlay's mosquito theory.

During the period of frequent epidemics which the Public Health Service was called upon to combat, a good many officers acquired yellow fever and recovered from it, thereby becoming condemned to further services in this field, since they were immunes and could be expected to keep on their feet during tours of such duty. Unfortunately a number died, mostly young men of promise at the very beginning of their medical careers; and it may not be out of place to record here, somewhat obscurely as in an overgrown country churchyard, their names and where and when they perished, that their brief epitaphs may be read on passing by.

Roswell Waldo, Cairo, Ill., 1878.
W. C. W. Glazier, Key West, Fla., 1880.
J. M. Greene, Key West, Fla., 1881.
J. F. Groenevelt, Chandeleur Island, 1891.
J. W. Branham, Brunswick, Ga., 1893.
Wm. R. McAdam, Key West, Fla., 1899.

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